Catalytic Asymmetric Synthesis of Chiral Alcohols and Amines

Development of a New Class of Chiral Catalysts

J.G.H. Willems

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EEN WETENSCHAPPELIJKE PROEVE OP HET GEBIED VAN DE NATUURWETENSCHAPPEN

PROEFSCHRIFT
TER VERKRIJGING VAN DE GRAAD VAN DOCTOR AAN DE KATHOLIEKE UNIVERSITEIT NIJMEGEN, VOLGENS BESLUIT VAN HET COLLEGE VAN DECANEN IN HET OPENBAAR TE VERDEDIGEN OP
DINSDAG 19 NOVEMBER 1996
DES NAMIDDAGS OM 3.30 UUR PRECIES

DOOR
JOHANNES GERARDUS HENRICUS WILLEMS
GEBOREN OP 17 APRIL 1966
TE NIJMEGEN

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The research described in this Ph.D thesis was financially supported by DSM Research, Geleen, The Netherlands.

Realisatie: Drukkerij Quickprint, Nijmegen

ISBN 90-9009977-8

Foto omslag: Leander

'Lord, I fall upon my knees
And pray that all my syntheses
May no longer be inferior,
To those conducted by bacteria'

Prof. Dr. D. Seebach

Voor ons petekindje Laurine

Paranimphen:	**Jeannet Hammink**
	Marco Hersmis

Op de voorpagina van dit proefschrift zijn 2 linkerhanden en hun spiegelbeelden weergegeven In het algemeen draagt de term '2 linkerhanden' een negatieve klank met zich mee, echter met deze 2 linkerhanden heb ik het biologisch zeer belangrijke verschijnsel van chirale herkenning ofwel 'chiral recognition willen visualiseren Naast deze betekenis hebben deze elkaar herkennende linkerhanden voor de spiegel voor mij ook een symbolische waarde, namelijk het afsluiten van een studie periode van ± 12 jaar aan de Universiteit van Nijmegen In die 12 jaar heb ik naast studenten, docenten en promovendi vele mensen mogen ontmoeten en het is dan nu ook tijd om een aantal van hen te bedanken en tegelijkertijd afscheid te nemen In de westerse wereld is het gebruikelijk dit te doen middels het schudden van handen, meestal rechterhanden, maar dat dit ook met 2 gespiegelde linkerhanden kan moge duidelijk zijn

Om te beginnen wil ik mijn ouders bedanken voor het feit dat zij in de eerste 2 decennia van mijn leven gezorgd hebben voor een studievriendelijk klimaat thuis, hetgeen er in belangrijke mate toe heeft bijgedragen dat ik op 18 jarige leeftijd kon starten met mijn studie scheikunde in Nijmegen

Ik dank mijn bazen Prof dr Binne Zwanenburg, Prof dr Roeland Nolte en dr Hans de Vries voor het in mij gestelde vertrouwen en de vrijheid die ik kreeg tijdens het onderzoek en bedank DSM Research voor de financiering van dit project Dat een iets strakkere vinger aan de pols vanuit het zuiden des lands en een iets intensievere communicatie misschien sneller tot het gewenste resultaat hadden kunnen leiden is vooral interessante kennis achteraf

Naast de oorspronkelijke onderzoek<opdracht, het zoeken naar een bereidingswijze van chirale amines (DSM project), is ook de synthese van chirale alcoholen geexploreerd Bij dit onderzoek zijn enkele stagiares en stafleden betrokken geweest en zonder hun bijdrage had dit boekje hier niet gelegen! Het spin off onderzoek ontstond bij een zoektocht naar nieuwe goed toegankelijke chirale katalysatoren Via een oude '*chemische liefde*' van ondergetekende, de aziridine-2-carbonzure esters, is dit onderzoek opgestart in 1992 Ariela Vaarhorst en Jan Dommerholt hebben na de gebruikelijke opstart-problematiek uiteindelijk de eerste hoopgevende resultaten verkregen Eind 1993 werden door Jeannet Hammink en door Jan Dommerholt de e e's van 92% en hoger bereikt Dat de aanhouder wint blijkt maar weer eens en ik wil jullie, naast natuurlijk Bertus Thijs, die als supervisor en motiverende kracht optrad, zeer hartelijk danken voor de enorme inzet tijdens dit project dat is beschreven in de hoofdstukken 3 en 4 Het heeft mijn leventje als assistent in opleiding een stuk blijer gemaakt Prof Zwanenburg wil ik danken voor het geloof in dit onderzoek in een vroeg stadium en de vrijheid die hij mij gegeven heeft om me naast mijn eigenlijke onderzoeksopdracht met dit werk te bemoeien

Met Bertus heb ik al te maken vanaf het allereerste uur van mijn opleiding tot organisch chemicus In september 1988 kwam ik in zijn groep, onder leiding van dr Johan Legters, aziridine-2-carbonzure esters het leven zuur maken Bertus' altijd durende enthousiasme, in het bijzonder waar het de chemie aangaat, heeft mij besmet en mede daardoor heb ik het na mijn stage in Bowling Green (USA) aangedurfd om als 'semi-wetenschapper A I O te worden in Nijmegen Bertus, ik wil je hartelijk danken voor de leerzame en gezellige tijd op en rond de kamers (k351/k352/k353) en denk nog vaak terug aan die ene avond in Kyoto dat zelfs jouw lever de grote aantallen baco s en jeco's niet meer aankon Verder dank ik je voor het minitieus doornemen van enkele hoofdstukken van dit proefschrift

Met het project dat vanuit het zuiden des lands werd geïnitieerd hebben zich achtereenvolgens drie heren bezig gehouden Henk Husken startte in september 1992 met reactie-kinetisch onderzoek aan '*zijn imine*' Henk heeft de benodigde infrastructuur rond dit onderzoek opgezet en ik dank je voor de tomeloze inzet die je aan de dag hebt gelegd Verder is voor reactie-kinetisch onderzoek precieze essentieel en voor jou waren gelukkig de cijfers achter de comma ook belangrijk Dat er met jouw komst op k351 ook af en toe klassieke muziek te beluisteren viel tussen het gebruikelijke '*pop non-stop*' geweld was leuk meegenomen!

André Lucassen, heeft het werk dat was uitgevoerd aan '*Henks imine*' herhaald voor zijn eigen imine substraat Verder bleek al snel dat zijn hart toch vooral bij het edele organisch chemische 'bak en braad' werk ligt en heeft hij een serie chirale '*azy-kats*' gesynthetiseerd! André, ondanks jouw interpretatie van het begrip orde en netheid kan ik terugkijken op een prima samenwerking Zeker ook de confrontaties tussen jou en Jeannet, die wel enige orde in k351 op prijs stelde, waren boeiend en zorgde ervoor dat niet ik continu als corrigerende factor hoefde op te treden!

In het laatste stadium van mijn promotieonderzoek heeft Marco Hersmis het initiele asymmetrische imine-isomerisatie-werk van André vervolgd en zijn eigen imine kinetisch onderzocht Marco's inzet en precisie waren hoog en zijn interesse in het meten van alles wat los en vast zit (FT-IR, GC-MS, NMR), zolang de meetapparatuur maar gekoppeld is aan een computer, waren zeer nuttig om gaten in het experimenteel gedeelte van mijn onderzoek op te vullen Marco, ondanks het feit dat je het bijna je gehele stage zonder mijn directe begeleiding hebt moeten stellen, omdat ik mijn dagen thuis al schrijvende sleet en later in Den Haag in de één na laatste lichting KLu-ROAG-ers (lichting 95-3) actief was, heb je een prima stuk onderzoek met de daarbij horende resultaten geleverd!

Samen zijn jullie goed geweest voor een fors stuk reactie-kinetisch en asymmetrische imine isomerisatie onderzoek, zoals beschreven is in hoofdstukken 5 en 6 van dit proefschrift Heel hartelijk bedankt allemaal! Ik heb veel van jullie allen geleerd, hopelijk jullie ook wat van mij!

Wim van Luyn dank ik voor zijn inzet tijdens de aanleg van de 'schlenk-lijn' op k351 Vele afdelingen en technische diensten moesten worden benaderd om uiteindelijk een perfecte zuurkast installatie op te leveren Een schlenk-lijn heeft ook het gebruik van nieuw schlenk-glaswerk tot gevolg De heren van de glasinstrumentmakerij onder leiding van Jos Haerkens zorgden ervoor dat k351 in hoog tempo van allerlei exotisch glaswerk werd voorzien! In het kader van het voornoemde 'schlenk gebeuren dank ik ook Wouter van den Berg zeer hartelijk voor nuttige tips bij de aanleg van de 'lijn' en het verzorgen van vele liters ultra-zuivere, ultra-watervrije en ultra-zuurstofvrije THF en andere essentiele oplosmiddelen die nodig waren in het imine isomerisatie onderzoek

Vanuit DSM hebben dr Hans de Vries als directe begeleider en dr Bernard Kaptein zich met het imine onderzoek bemoeid De 3-6 maandelijkse meetings in Geleen of Nijmegen gaven mij de mogelijkheid om mijn onderzoeksvorderingen te presenteren Ondanks het feit dat deze vorderingen, zeker in het begin, in een zeer laag tempo verliepen zijn jullie toch blijven luisteren In een later stadium bleek het van essentieel belang om over een snelle en accurate e e bepalings methode te beschikken en heeft dr Lucien Duchateau (DSM) in korte tijd een uitstekende HPLC methode gevonden (hoofdstuk 7) E e-bepalingen met behulp van HPLC apparatuur brengen het gebruik van '*chirale kolommen*' met zich mee en samen met Jean-Paul Seerden is het gelukt om die enkele zeer dure chirale kolommen die de afdeling rijk was nuttig te gebruiken en heel te houden René Aben dank ik voor de gastvrijheid als ik weer eens kwam sleutelen en zeuren over niet functionerende HPLC apparatuur op k360

Dr Gerry Ariaans dank ik voor de adviezen met betrekking tot mijn onderzoek, chiraliteit in het algemeen en allerhande 'computer crap waarvan ik meestal meer dan de helft niet begreep en ik kijk met plezier terug op onze deelname aan the 5th International Symposium on Chiral Discrimination te Stockholm in september 1994 Gerry, de combinatie van computer allesweter en

jouw 'chinchilla fokkerij' heeft mij altijd enigszins verbaasd, echter toen ik hoorde dat die beestjes gemiddeld een kuub hout en printer-papier per jaar consumeren werd mij ineens veel duidelijk! Verder ben ik jou en dr Bernard Kaptein erkentelijk voor jullie beider optreden in de manuscript commissie en dank ik jullie voor de correcties en suggesties.

Dr René de Gelder dank ik voor het opnemen van de *X-rays* van de nieuwe *kats* zoals die in hoofdstuk 3 zijn weergegeven en het leveren van vele plaatjes van deze wonderschone moleculen voor dit proefschrift en het artikel betreffende dit onderwerp

De groepen Zwanenburg, Klunder, Thijs, Nefkens, Chittenden, Scheeren, Nolte, Feiters, Tesser, collega A I O's, O I O's, 'post docs', studenten en stagiaires dank ik voor de prima sfeer op de afdeling organische chemie in Nijmegen De vele activiteiten die werden georganiseerd naast het werk, van bowlen tot golfen, zwemmen, skien in Winterberg, paardrijden (eens maar nooit weer, Petra!) en onze unieke en onvergetelijke Japanreis in 1992, hebben het leven op en buiten de afdeling zeer aangenaam gemaakt!

Naast de collega's en studenten wil ik ook de mensen van de analytische groep betrekken in mijn dankzegging Ad Swolfs voor het altijd tussendoor opnemen van 400 MHz NMR spectra die in het beginstadium van het onderzoek essentieel waren om de e e's van de enkele chirale *kats* te bepalen Ik heb niet vaak een beroep op je gedaan maar als ik kwam dan waren de samples vaak dezelfde dag nog gemeten! Pieter van der Meer en Helene Amatdjais voor de hulp bij het opstarten voor onder het stof geraakte HPLC apparatuur en Peter van Galen voor de vrijheid die ik en later één van de studenten kreeg bij het gebruik van de nieuwe GC/MS apparatuur Bij Chris Kroon kon ik altijd terecht voor chemicalien en gassen die nodig waren voor de GC- en HPLC apparatuur Ietje Dorhout, Sandra Tijdink, Leyla Karakas en Nelly Weustink dank ik voor administratieve zaken, AB-bonnen voor treinkaartjes naar 'belangrijke meetings', versturen van Fax-messages etc In de allerlaatste fase, toen ik al weer gepromoveerd was tot *burger*, kon ik bij Sandra Tijdink en Jacky Versteeg terecht (vaak telefonisch) om te informeren over de 'correctie toestand' van mijn proefschrift en zij zorgden ervoor dat de gecorrigeerde versies in Bergen op Zoom terecht kwamen

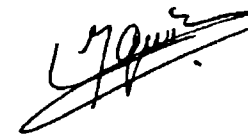
Henk Herms, bibliothecaris, zorgde er voor dat ik in de 'bieb' alles snel kon vinden en dat de aangevraagde artikelen in record tijd (soms al binnen 5 minuten) op mijn bureau lagen Hans Adams dank ik voor het feit dat ik gebruik kon maken van de Mac en HP-Laserjet op zijn kamer, een combinatie die "tig" versies van dit proefschrift heeft uitgeprint met 600 dpi resolutie Hans door jouw goede management aangaande de aanwezigheid van printer cartridges, dozijnen dozen papier en andere zaken die essentieel zijn voor het produceren van een proefschrift, kwam ik nooit voor niets naar de Uni

Tot slot dank ik vrienden, familie, schoonfamilie en kennissen die af en toe wilden luisteren naar verhandelingen over links- en rechtsdraaiende moleculen en het belang van dit 'draaien' voor het functioneren van organismen Zelf kon ik naar hieve lust kappen en draaien met de heren van het 2e-klasse zaalvoetbalteam HOOGMA 1, in een later stadium gesponsord door de *'concurrent'* drankenhandel "in de blauwe druif" (het was effe wennen) Hier raakte ik mijn overtollige energie kwijt tijdens trainingen, wedstrijden, 'bierbeurten', 'trainingskampen' te Langweer en de jaarlijks terugkerende weekenden, op door aanwijzingen te raden locaties Verder heb ik heel wat zang uren achter de rug met het DEO jongeren koor Dat we de laatste jaren moesten vechten tegen de bierkaai om te zorgen voor een enigszins 'uitgebalanceerd' koor op de zondagmorgen heeft me af en toe moedeloos gemaakt Het heeft me ook zeer veel plezier gedaan dat zowel de 'jonge garde' als de wat 'oudere jongere garde' het nog zo lang hebben volgehouden

In de tijd dat ik bij de Koninklijke Luchtmacht als dienstplichtig reserve-officier Afval Registratie Systemen (ARS) mocht inventariseren, heb ik enkele maanden in Bilthoven bij mijn schoonouders gebivakkeerd om aldaar in de avonduren en vele weekends aan de afronding van dit proefschrift te kunnen werken Jan en Ans, hartelijk dank voor jullie gastvrijheid in die maanden,

die zeker hebben bijgedragen aan een forse tempoversnelling in het gereedkomen van dit proefschrift!

Lest en zeker ook the best; Lieve Carolijn, je had het zeker in de eerste 2 jaar van mijn promotieonderzoek zwaar om bij mij de motivatie er in te houden, maar gelukkig heeft beider doorzettingsvermogen geloond; Het boekje is af! Vanaf nu kunnen we weer elk weekend naar Parijs!!



Geert- Jan

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Chapter 2

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Part B: Imine isomerization reaction

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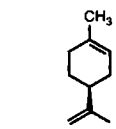
General Introduction

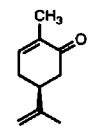
1.1 The importance of chiral compounds in nature

Chirality is an intrinsic phenomenon in nature, and molecular asymmetry plays an important role in science and technology. The word "chiral" has its origin in the Greek word for hand. The French physicist Biot[1] discovered the phenomenon of optical activity in 1815 as the ability of a substance to rotate the plane of polarization of light. Subsequently, Louis Pasteur, a student of Biot, proposed[2] in 1848 that a large number of organic substances have two possible structures which, like a pair of hands, are nonsuperimposable mirror images of each other. The origin and control of this handedness or chirality is an important area of current research.[3]

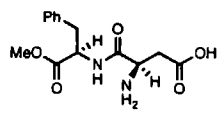
A wide range of significant biological functions emerge through molecular recognition, which often requires strict matching of chirality. Two enantiomers have identical physical and chemical properties. When placed in a chiral environment however, they can exert different chemical reactivities. This means that a chiral species can, at least in principle, differentiate between the two enantiomers through covalent or non-covalent diastereomeric interactions. This phenomenon is referred to as chiral discrimination or chiral recognition, similar to the match of a left hand and a left hand glove.



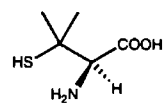
(S)-**1**
Limonene
(S): lemon odor
(R): orange odor



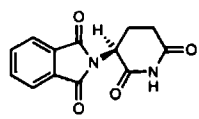
(S)-**2**
Carvone
(S): smells like caraway
(R): smells like spearmint



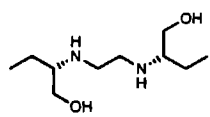
(R,R)-**3**
Aspartame
(S,S): sweet
(R,R): bitter



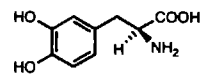
(S)-**4**
Penicillamine
(S): antiarthritic drug
(R): mutagenic properties



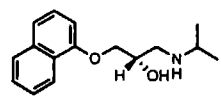
(S)-**5**
Thalidomide
(S): teratogenic effects
(R): sedative drug



(S,S)-**6**
Ethambutol
(S,S): tuberculostatic drug
(R,R): causes blindness



(S)-**7**
DOPA
(S): anti-Parkinson drug
(R): causes serious side-effects



(S)-**8**
Propanolol
(S): high activity
(R): low activity

Figure 1.1

Since biological systems recognize the members of a pair of enantiomers as different substances, enantiomers, in most cases, will have a different response in these systems. It has been shown for many pharmaceuticals that only one enantiomer contains all desired activity, whilst the optical antipode is either totally inactive (isomeric ballast) or toxic.[4] Numerous

examples of the different biological effects of enantiomers are reported and some examples are depicted in Figure 1 1 One of the enantiomers of limonene (**1**) smells of lemons, and the other of oranges One enantiomer of carvone (**2**) smells of caraway, the other of spearmint These differences obviously are of importance for the perfume and flavour industry The dipeptide ester aspartame (**3**) is used as a low-calorie sweetener in soft drinks The molecule consists of the two amino acids L-aspartic acid, which is tasteless and L-phenylalanine, which is bitter Together, both amino acids form a dipeptide with an intense sweet taste, that is approximately 160 times sweeter than sucrose One enantiomer of penicillamine (**4**) exhibits antiarthritic properties but the other is highly toxic The sad example of thalidomide (**5**) in the early 60s, which in its R-form is a sedative drug and in its S-form causes teratogenic effects in the human fetus, is well known [5] Recent publications on thalidomide reveal however, that even under 'mild' chemical conditions, like a physiological environment, the drug undergoes a transformation from one pure enantiomeric state to a racemic one with surprising ease (half life of racemization is 2 5 h) [6] This observation suggests that administration of thalidomide in enantiopure form is of no practical use because of racemization under biological conditions An example where one enantiomer exhibits toxic side-effects and therefore the drug can only be administered as an enantiomerically pure compound[7] is the R,R enantiomer of ethambutol (**6**) that causes blindness, whilst the antipode is a tuberculostatic agent The D-enantiomer of L-DOPA (**7**) causes serious side-effects, such as granulocytopenia,[8] whilst L-DOPA is used for treatment of Parkinson's disease In some cases however, both enantiomers of a therapeutic drug have a desirable, but different therapeutic effect just as encountered for many natural products e g , pseudo enantiomers quinine and quinidine [9]

Until recently, it was common practice for a pharmaceutical company to market a chiral drug as the racemate, and as recently as 1985, more than 75% of chiral drugs were sold as the racemate [10] This policy implies that each dose of a drug is contaminated with an equal amount of an isomer, which usually has no therapeutic value but may have the potential to cause unsuspected deleterious side effects

From the aforementioned facts, which form the basis for the current trend toward stereochemically pure drugs, one could easily get the impression that racemates always have to be considered as 'bad' from a medical point of view This is, however, not always true, and some cases have been reported, which show synergistic effects of enantiomeric compounds [11] An example of a drug demonstrating this effect is the β-blocking agent propanolol (**8**), which shows an increase in half life, ultimately leading to a reduction of the required dose, when administering the drug as a racemate [12] It should be stressed, however, that any racemate consists of a mixture of chemical entities, which despite their close structural relationship, must be regarded as different pharmacological species, either displaying desired or undesired effects [13]

Recent rulings of the Food and Drug Administration (FDA) in the United States reflect the current situation in "chiral drugs' pharmaceutical industries will have to provide rigorous justification to obtain the FDA's approval of racemates [14]

1.2 Routes toward enantiomerically pure compounds

There are several methods to obtain enantiomerically pure materials, which include classical optical resolution via diastereomers, chromatographic separation of enantiomers, enzymatic resolution, chemical kinetic resolution, chiral pool synthesis, fermentation and asymmetric synthesis In this paragraph several methods to obtain enantiomerically pure compounds are briefly described [15] The four main routes for the synthesis of enantiomerically pure compounds are

1: *via the resolution of racemates*
2: *from enantiomerically pure natural products (starting materials from the so-called chiral pool)*
3: *via fermentation*
4: *via asymmetric synthesis*

The resolution of racemates via preferential crystallization of diastereomeric salts or covalently bonded diastereomers,[16] is the oldest[17] and still the most important method in obtaining enantiomerically pure compounds in the industry. In resolution by differential crystallization a racemic product mixture is converted into a separable mixture of diastereomers with the use of a stoichiometric amount of an optically pure resolving agent. This method, however, requires recovery of the resolving agent and wastefully consumes starting materials and reagents in order to prepare 50% of the unwanted enantiomer, which must then be racemized or discarded.

Classical resolution becomes particular attractive when it can be combined with an *in situ* racemization in a crystallization-induced asymmetric transformation, a process which is called 'deracemization'.[18] Using this deracemization procedure, it is possible to design a process with almost complete conversion to the required enantiomer, and it lacks the disadvantage of classical resolution procedures. It has become a powerful procedure in the production of enantiomerically pure molecules in the industry in the last decade and some examples are described by Merck[19] and DSM.[20]

Another important strategy in the preparation of enantiomerically pure compounds is the enzymatic and chemical kinetic resolution of racemic substrates. Especially enzymes are nowadays generally accepted as tools in organic synthesis in universities and the industry.[21] Enzymes catalyze many reactions under often very mild reaction conditions, and they are generally very selective with regard to the type of reaction they catalyze and with respect to the structure and stereochemistry of the substrate. Several reviews on the application of biocatalysts in organic synthesis have appeared.[22]

The commercially available enantiomerically pure compounds, such as α-aminoacids, steroids, carbohydrates, alkaloids, and terpenes are important starting materials in asymmetric synthesis. Well designed transformations and syntheses starting from these chiral compounds (known as the 'chiral pool') resulted in a large number of new enantiomerically pure compounds over the years, many of which are now commercially available. This approach is limited by the availability of inexpensive starting materials with the right sense of chirality and with close structural similarity to the final target.[23]

Another old industrial method for the synthesis of optically active compounds is fermentation, which is defined as a transformation mediated by growing microorganisms.[24] Many fermentations are complex multistep reactions, involving several different enzymes of living cell systems. Enzymatic transformations, on the other hand, generally involve a single step performed by one enzyme and the whole machinery of the cell is not necessary. There has been a growing interest in the use of fermentation procedures for the preparation of enantiomerically pure compounds like amino acids, β-lactam antibiotics, and vitamins. An important drawback of enzymatic and fermentation processes is that only one of the two possible enantiomers can be prepared with this methodology. If the other enantiomer of the target molecule has to be prepared, other microorganisms or enzymes have to be found in order to obtain this optical antipode.

Asymmetric synthesis, especially asymmetric catalytic synthesis, has the attractive feature of, at least in principle, a high turn-over of chirality. Under well chosen conditions, many chiral product molecules can be produced by one catalyst molecule. This aspect of multiplication of chirality is characteristic for both biocatalysis and catalysis by synthetic chiral catalysts. Enantioselective catalysis has become a useful method and can often provide an alternative to

biocatalysis.[25] Synthetic chiral catalysts have some advantages over enzymes. First of all synthetic catalysts can promote reactions that are not known to occur in nature. Secondly, the chirality or handedness of a synthetic catalyst can be changed relatively easily by using the antipode as the starting material in its preparation. In most cases, essential chiral intermediates in the preparation of chiral catalysts are taken from the chiral pool and often both enantiomers are available. Thirdly, substrates that are not accepted in enzymatic reactions may be used in reactions catalyzed by synthetic catalysts. In many cases, high substrate concentrations can be used, and the separation and recovery of products are relatively easy as compared to enzyme catalyzed reactions that are often performed in aqueous or near aqueous environments. Finally, in many cases synthetic catalysts have a higher stability than enzymes, which are often very sensitive to degradation caused by heat, oxidation, and pH.

1.3 Asymmetric synthesis

Emile Fischer[26] already discussed the phenomenon of asymmetric synthesis as early as 1894. Asymmetric synthesis can be devided into two main fields: enantioselective synthesis and diastereoselective synthesis. The former which involves the reaction of a prochiral molecule with a chiral substance forms the main topic of this thesis. The latter deals with the preferential formation of a single diastereomer by the creation of a new stereogenic center in a chiral molecule.

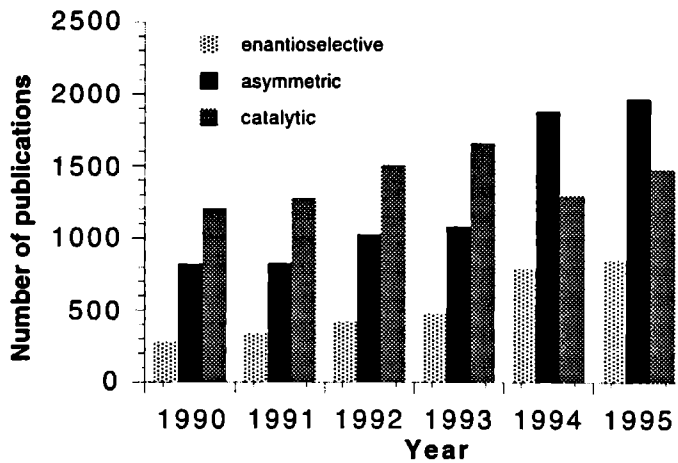


Figure 1.2

The increasing current interest in this field is attributable to the development of new and more efficient methods in asymmetric synthesis in the past 10-15 years. The number of publications dealing with "asymmetric synthesis" published in the 10 years after the book by Morrison and Mosher[27] (1971) was almost the same as that of all papers published before 1971. This increase in output clearly shows the attention paid to this important topic in this period. In the 1980s, research on asymmetric synthesis became even more important, since enantiomerically pure compounds were required for the total synthesis of natural products, pharmaceuticals and agricultural agents. The still growing interest in asymmetric synthesis over the years 1990-1995 is depicted in Figure 1.2. These data were obtained by monitoring the annual number of publications (Current Contents on CD-ROM disc) with the keywords "enantioselective, asymmetric and

catalytic" in title and abstract Several books reviewing this important topic have appeared over the years [28]

In this thesis the enantioselective synthesis of chiral alcohols and amines (via imine intermediates) using new chiral catalysts is described These asymmetric reactions are pictured in Figures 1 3 and 1 4, respectively The prochiral ketone (Figure 1 3) and the prochiral aza-allyl anion (Figure 1 4) can be approached by a H^--ion and a H^+-ion, respectively, from either the Re site or the Si site [29]

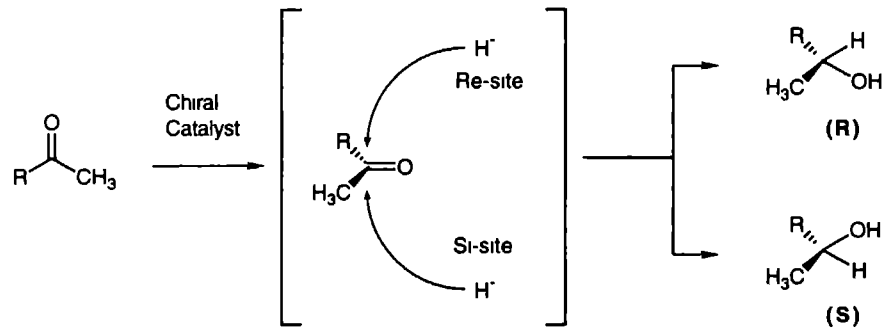


Figure 1 3

When no chiral source is used, the reaction intermediate related to the transition states TS# of either approach will be enantiomeric, which results in a racemic product When a chiral catalyst is used, the transition states TS# become diastereomeric and when the catalyst is well chosen, this may result in an excess of one enantiomer over the other and the reaction is called enantioselective

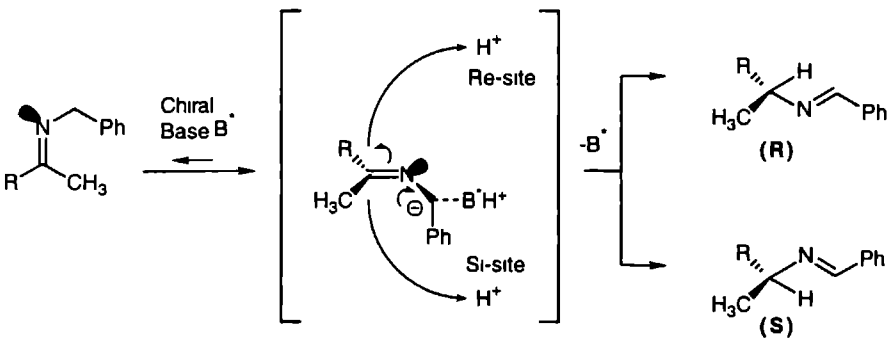
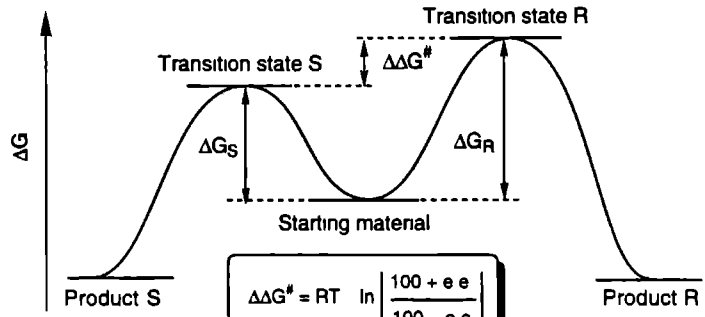


Figure 1 4

The free energy profile of an enantioselective reaction is shown in Figure 1 5 The difference between the two free energies of activation ($\Delta\Delta G^{\#}_{R\text{-}S}$) is related to the enantiomeric excess (e e) of the product For a $\Delta\Delta G^{\#}_{R\ S}$ of 17 1 kJ/mol between the two diastereomeric transition states, an e e of 99 8% is obtained in the asymmetric reaction (Figure 1 5) The enantiomeric excess is defined as e e (%) = (R-S)/(R+S) x 100% A second property of a product to indicate the selectivity of a reaction is the optical purity (o p) The optical purity is defined as o p (%) = ($[\alpha]/[\alpha]_{(enantiomerically\ pure)}$ x 100% As shown by Horeau,[30] a linear relationship between the enantiomeric excess and the optical purity is not always observed

The advantage of *catalytic* asymmetric synthesis over *non-catalytic* asymmetric reactions is that in catalytic processes one chiral catalyst molecule is able to generate many chiral product molecules, just as enzymes do in biological systems Examples of important achievements in this field are the asymmetric catalytic hydrogenation of dehydroamino acids, as described by Knowles et al [31], the

Sharpless epoxidation,[32] the Sharpless dihydroxylation[33] and the second generation asymmetric catalytic hydrogenation process developed by Noyori et al [34] Catalytic asymmetric synthesis has economic and environmental advantages over stoichiometric asymmetric synthesis for industrial scale production of enantiomerically pure compounds



ΔΔG#(298K) kJ/mol (kcal/mol)	0	3 44 (0 82)	5 46 (1 30)	7 85 (1 87)	11 4 (2 71)	17 1 (4 07)
S / R	50 / 50	80 / 20	90 / 10	96 / 4	99 / 1	99 9 / 0 1
e e (%)	0	60	80	92	98	99 8

Figure 1 5

A number of catalytic asymmetric reactions, including the asymmetric isomerization during the synthesis of L-Menthol, and the asymmetric cyclopropanation were commercialized in the 1980s by Takasago[35] and Sumitomo,[36] respectively The asymmetric hydrogenation during the synthesis of L-DOPA was established in the early 1970s by Monsanto [37] A modified L-DOPA process was developed by Selke and coworkers[38] and commercialized in the early 1980s by VEB Isis Chemie,[39] using a similar procedure as in the Monsanto process

Research on new catalytic asymmetric reactions will continue far beyond the turn of the century, and new catalytic asymmetric processes will be important in the chemical technology of the future The industrial aspects of the synthesis of enantiopure products have been reviewed in two recent books [40]

1.4 Aim and outline of this thesis

The strategy used in the enantioselective synthesis of chiral alcohols and amines is depicted in Figures 1 3 and 1 4, respectively The aim of the first topic was to evaluate the potential of new chiral oxazaborolidines derived from aziridine carbinols in asymmetric reduction reactions The enantioselective synthesis of amines has its origin in an asymmetric proton transfer by means of a chiral base

In chapter 1 an introduction on chirality in general is presented In addition, a brief overview of the synthetic approach to enantiomerically pure compounds is given

In chapter 2 a survey of the pertinent literature on the catalytic asymmetric synthesis of chiral alcohols and amines is described An introduction to the imine isomerization reaction is also given The results obtained by Ingold in the 1930s and Cram in the 1960-70s are briefly reviewed

Chapter 3 deals with the synthesis and characterization of a new class of chiral catalysts derived from aziridine-2-carboxylic esters An improved multi-gram scale synthesis of aziridine-2-carboxylic esters, the precursors of the new aziridine-2-carbinol catalysts, is described.

In chapter 4 the synthesis of a series of new aziridine-2-carbinol catalysts and their use in the asymmetric catalytic reduction of prochiral ketones (Figure 1 3) is described

The second topic of this thesis deals with the synthesis of chiral amines using an asymmetric imine isomerization reaction (methylene azomethine rearrangement) in the key step (Figure 1 4) Chapter 5 describes a kinetic study of the imine isomerization reaction using an achiral base, and a mechanism for this reaction is proposed.

The asymmetric catalytic imine isomerization is described in chapter 6. The correlation between the rates of isomerization and racemization of the imines and the catalytic abilities of several chiral bases in this reaction is investigated

Chapter 7 deals with the development of an accurate and fast method for the determination of enantiomeric purities of chiral imines and the corresponding amines using HPLC techniques

This thesis is concluded with a summary in English and Dutch.

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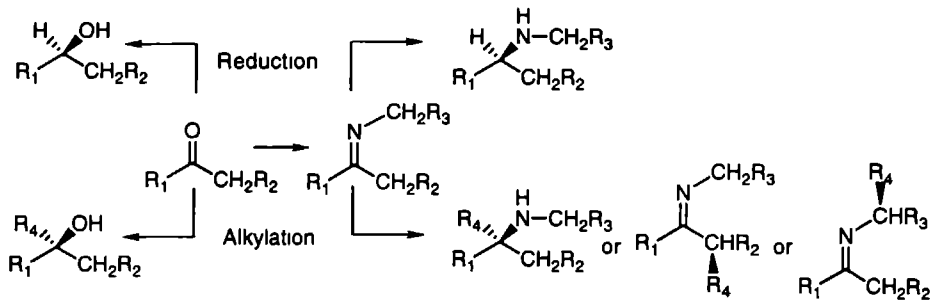
Chapter 2

Asymmetric Synthesis of Chiral Alcohols and Amines

A survey of relevant literature

2.1 Introduction

The synthesis of chiral alcohols and amines has received much interest, because these compounds have found use as chiral building blocks in the synthesis of enantiomerically pure drugs, natural compounds and as resolving agents Various strategies in the asymmetric synthesis of chiral alcohols and amines are shown in Schemes 2 1 and 2 2 In Scheme 2.1, the target molecules are prepared starting from ketones and imines by either an asymmetric reduction or an alkylation reaction These reactions can be devided into two classes,[1] *viz* enantiodifferentiating and diastereodifferentiating reactions In the former, chirality is induced by an external, optically active catalyst and a prochiral ketone and imine are used as starting material (R_2 = achiral unit) In the latter, the chiral inductor is built into the substrate, induces chirality in the diastereotopic part and after removal of the inductor an enantiomerically enriched molecule can be obtained (R_2 = chiral unit)



Scheme 2.1.

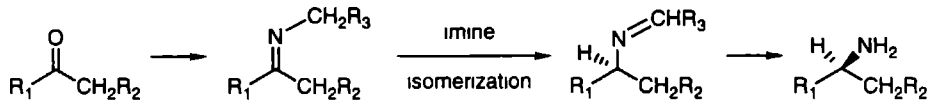
In the synthesis of chiral amines from imine intermediates, literature reports show that in the asymmetric alkylation of imines, diastereodifferentiating methods are used in most cases This diastereoselective strategy, although lacking the advantages of a catalytic process, has become an important tool in the alkylation of a variety of imines

To date only a few efficient processes for the alkylation of imines using catalytic amounts of external chiral ligands are described [2] Therefore, the development of catalytic methods remains a worthwhile challenge in the asymmetric synthesis of chiral amines from imine intermediates

Impressive results have been achieved in the asymmetric alkylation of aldehydes Several reviews on this topic appeared between 1988 and 1995.[3] However, the asymmetric alkylation of aldehydes and imines will not be discussed in detail, because this type of reactions is beyond the scope of this thesis

This literature survey is devided into two parts the first part deals with the asymmetric synthesis of chiral alcohols and amines starting from prochiral ketones and imines using reductive methods (part A) A brief review on the asymmetric transition metal catalyzed reactions in the reduction of ketones and imines and the future prospect of this technology is given in section 2 4 A summary of the relevant literature on the asymmetric catalytic synthesis of chiral alcohols and amines using chiral oxazaborolidines published up to January 1996, is the subject of section 2 5

The second part (part B) deals with the mechanism of the imine isomerization reaction In Scheme 2 2 this alternative strategy in the asymmetric catalytic synthesis of chiral amines from prochiral ketones via imine intermediates is depicted



Scheme 2 2

The mechanism of the imine isomerization reaction was extensively studied by Ingold in the 1930s, by Ossorio in the 1950s and by Cram in the 1960-70s using achiral bases

Part A Asymmetric reduction of ketones and imines

2.2 General considerations

Catalysis can be performed using heterogeneous and homogeneous reactions conditions A chiral environment in heterogeneous catalytic processes may be obtained by binding a metallic active phase on a chiral support (*e g* biopolymers such as polypeptides, polysaccharides, and cellulose) or by absorbing a chiral modifier onto the active phase of a conventional metallic catalyst [4] The first technique was explored by Schwab and coworkers in 1932, who examined metals supported on cleaved quartz surfaces which resulted in relatively low e e 's of the product [5] In the late 1930s hydrogenation of unsaturated compounds using metallic catalysts deposited on a chiral support[6] were reported

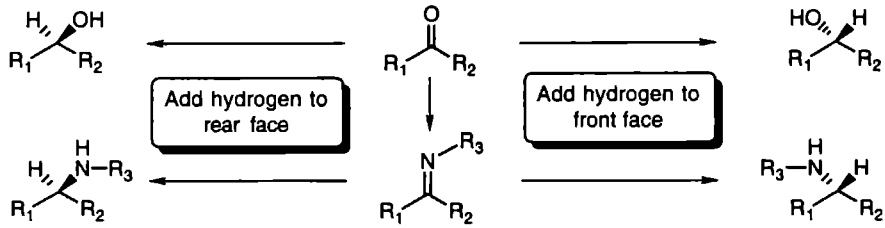
The second technique was introduced by Lipkin and Stewart in 1939, who reported the use of Raney Ni modified by glucose and Pt modified by the alkaloid cinchonine [7] When the enantioselectivity using this methodology exceeded 60% e e in the 1950s, this catalysis under heterogeneous reaction conditions became increasingly popular Recently, Blaser and others[8] developed remarkably effective processes for the heterogeneous enantioselective hydrogenation of α-ketoesters using cinchona modified heterogeneous platinum catalysts

Heterogeneous enantioselective catalysis is still an interesting area of modern chemistry Most industrial reductions require heterogeneous catalysts, which are easier to handle and to scale-up Recently, several prochiral ketones have been reduced by hydride-transfer reactions catalyzed by a heterogeneous enantioselective catalyst [9] Several reviews covering this field have appeared [10] This survey is focussed on the asymmetric catalytic synthesis of alcohols and amines under homogeneous reaction conditions

2.3 Asymmetric reduction using chirally modified hydride reagents and catalysts

Asymmetric transformations involve the conversion of a prochiral substrate (ketone, imine) into a chiral product (alcohol, amine) For ketone and imine reductions this is achieved by the overall addition of hydrogen to one face of the carbonyl or imine moiety as shown in Scheme 2 3

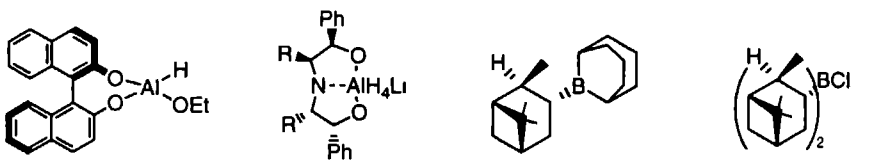
An attractive manner to perform an asymmetric reduction is the use of a hydride source with a built-in chiral center which can induce the chirality transfer Two types of reagents that give high enantiomeric excesses in asymmetric reductions are chirally modified $LiAlH_4$, and organoboranes Lithium aluminium hydride has been modified by various chiral alcohols,[11] amines, and ethanolamines [12]



Scheme 2 3

Reduction products with e e 's ranging from a few percent to over 90% have been reported [13] Some representative examples of chiral aluminum hydride reagents (**1** and **2**) are shown in Figure 2 1

Other interesting reagents are enantiomerically pure organoboranes as were first described by Midland et al [14] in 1980 Among these reagents Alpine-Borane (**3**), developed by Midland, and chlorodialkylborane (DIP-Chloride) (**4**), developed by Brown et al [15] are the most selective Organoboranes **3** and **4** constitute another type of reducing agent in comparison with the chiral aluminum hydrides described above



(R)-BINAL-H (**1**) Diethanolamines (**2**) Alpine-borane™ (**3**) DIP-Chloride™ (**4**)

Figure 2 1

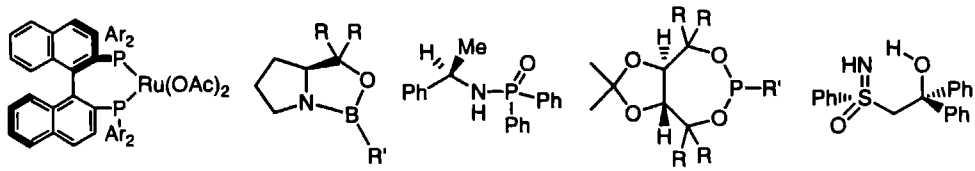
They react with prochiral ketones under the formation of a ketone-borane complex The asymmetric transfer of a hydride from the chiral borane reagent is followed by the release of the chiral olefin In case of **3** and **4** the olefin that is released is α-pinene DIP-Chloride enjoys an increasing number of applications in the reduction of aryl-alkyl ketones and β-amino ketones [16] The synthesis of either enantiomer of the current widely used anti-depressant drug fluoxetine hydrochloride (Eli Lilly Prozac™) by DIP-Chloride was reported [17]

All reagent systems **1-4** as described above have a serious drawback They all need to be used in stoichiometric amounts and consequently one mole of reagent is required for the reduction of one mole of substrate In the synthesis of relatively small amounts of enantiopure natural products the stoichiometric use of chiral reagents is acceptable However, for industrial purposes the use of stoichiometric amounts of reducing reagents may not be possible due to high costs and environmental problems associated with large quantities of these materials Therefore, much effort has been devoted to develop catalytic chiral reagents

For the catalytic asymmetric reduction of prochiral ketones to chiral alcohols several efficient catalysts have been described and most of them fall into one of two major categories, *viz i)* transition metal catalysts modified by chiral ligands[18] such as **5** and *ii)* oxazaborolidine derivatives[19] such as **6** These catalysts will be described in sections 2 4 and 2 5, respectively

With the first class of catalysts chiral products of high enantiomeric purity may be obtained, but the use of these catalysts is limited to functionalized ketone substrates, *viz* β-keto esters and

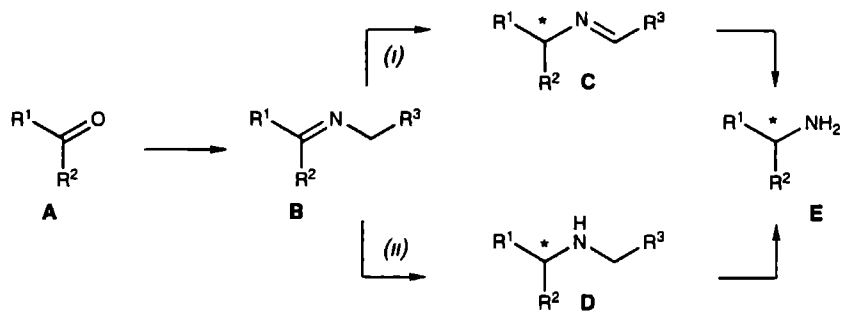
1,3-dıketones The second group of catalysts are effective for a broader range of ketones Recently, novel borane based carbonyl reduction catalysts derived from α-methylbenzylamine **7**,[20] diethyl-tartrate (DET) **8**,[21] and β-hydroxy sulfoximines **9**[22] have been reported



5 **6** **7** **8** R = Ph, 2-naphthyl; R' = Me, Ph, 2-naphthyl **9**

Figure 2 2

In the catalytic synthesis of amines using imine intermediates, various efficient catalyst systems have been developed For the synthesis of amines from their corresponding carbonyl compounds several methods have been reported,[23] and two of them are depicted in Scheme 2 4 The first one involves the conversion of ketones (**A**) into imines (**B**)[24] and enamines,[25] and subsequent reduction to the corresponding amines (**E**) has been accomplished by trichlorosilane /BF_3-OEt_2,[26] di(o-aminophenyl) disulphide (DAPDS)/ HBr,[27] and $RuCl_2(PPh_3)_3$/2-propanol[28] producing racemic amines (**E**) Alternatively, a ketone (**A**) can be subjected to a reductive amination procedure via **B** as intermediate yielding **D** (route (*ii*)) for which several methods and reagents have been reported, *viz* catalytic hydrogenation,[29] formic acid,[30] zinc/acetic acid,[31] metal hydrides,[32] sodium cyanoborohydride,[33] or sodium triacetoxy-borohydride [34] An asymmetric reductive amination procedure for the synthesis of chiral amines is very attractive Some examples are known, *e g* using chiral transition metal catalysts[35] and using hydrogen donors such as alcohols and acids as the source of hydrogen atoms[36] in an asymmetric transfer hydrogenation process



Scheme 2 4

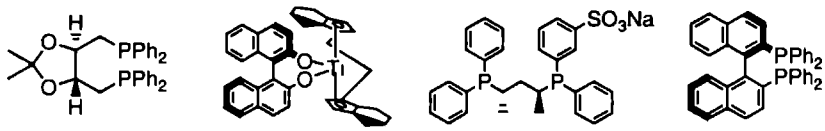
Another approach to the synthesis of amines from imine intermediates involves a base catalyzed double bond migration (route (*i*), from **B** to **C**) A literature survey on the mechanism of this imine isomerization reaction is given in section 2 6 An asymmetric double bond migration can be envisaged when this strategy is applied to prochiral imines (**B**) and some examples are given in section 2 7

Methods for asymmetric reduction of carbonyl and imine compounds with heterogeneous metal catalysts,[37] stoichiometric quantities of chiral reagents,[38] and biochemical methods[39] have been extensively reviewed in recent years, but are not included in this chapter, as they are beyond the scope of this thesis

2.4 Asymmetric hydrogenation using chiral transition metal catalysts

The asymmetric synthesis of chiral alcohols from prochiral ketones can be performed by hydrogenation using transition metal catalysts modified by chiral ligands In 1968 the homogeneous asymmetric hydrogenation of dihydroamino acid derivatives using Rh complexes with chiral tertiary phosphines was independently reported by Knowles[40] and Horner [41] Their results form the basis of Monsanto's asymmetric synthesis of the anti-Parkinson's drug L-DOPA

Many of the successful chiral ligands used for the transition metal catalyzed reductions are chelating phosphines with a C_2-symmetry axis, whereby the number of possible competing diastereomeric transition states, which occur during an asymmetric catalytic reaction, is reduced A review[42] on C_2 symmetry in asymmetric induction appeared in 1989



(R,R)-DIOP (**10**) **11** SKEWPHOS (**12**) (R)-BINAP (**13**)

Figure 2 3

The first high enantioselectivities in the asymmetric hydrogenation of dehydro amino acids (e e > 90%) were reported by Kagan[43] using DIOP (**10**) The asymmetric reduction of various functionalized ketones has been performed by Ru-BINAP (**13**) complexes with high enantioselectivities [44] It was found that Ru-BINAP catalysts are unable to hydrogenate simple ketones, because they lack the heteroatoms which are necessary for anchoring the Ru metal Recently, the enantioselective hydrogenation of simple aromatic ketones catalyzed by a BINAP-Ru(II) complex-chiral diamine-KOH system with high enantioselectivities (up to 98%) was reported by Noyori et al [45]

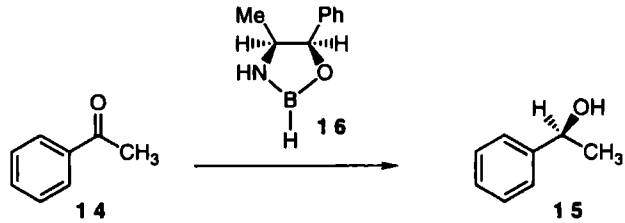
In the hydrogenation of benzylimines derived from acetophenones in the presence of rhodium complexes of chiral phosphines,[46] moderate enantioselectivities were obtained Hydrogenation of benzylimines derived from acetophenones by water soluble sulfonated SKEWPHOS ligands (**12**) in a two phase system were reported by Bakos et al [47] and de Vries et al [48] in 1991 and 1992, respectively Recently, highly enantioselective hydrogenations of imines,[49] cyclic imines,[50] and enamines[51] with e e 's up to 98% using a chiral titanium catalyst **11** derived from binaphtol were reported by Buchwald et al [52] Several reviews[53] and books[54] on catalytic asymmetric hydrogenation have been published

2.5 Enantioselective reduction using chiral oxazaborolidines

Chirally modified borohydrides serve as a useful catalyst system in the reduction of prochiral substrates Asymmetric reduction using optically active borane complexes was explored by Fiand and Kagan in 1969 In a first report on the use of chiral amine borane complexes, stoichiometric amounts of ephedrine boranes (**16**) were employed as catalysts in the reduction of acetophenone (**14**) to 1-phenylethanol (**15**)[55] (e e =3-5%) (Scheme 2 6) Related amine boranes in the presence of boron trifluoride etherate gave a somewhat improved enantioselectivity (e e =20%) [56]

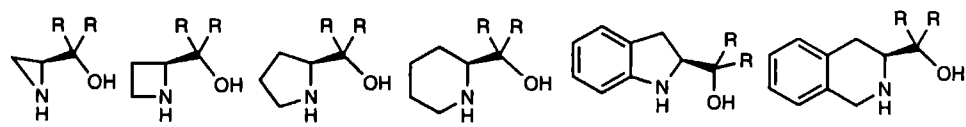
The asymmetric reduction of ketones by amino alcohol-borane complexes as reported by Itsuno et al in 1981,[57] contributed to the development of chiral oxazaborolidine catalyzed reductions Chiral oxazaborolidines catalyze a wide variety of reactions, such as the asymmetric reduction of ketones,[58] Lewis acid catalyzed cycloadditions,[59] aldol condensations,[60] organozinc

additions to aldehydes,[61] 1,3-dipolar cycloadditions,[62] and cyanohydrin formation.[63] Two reviews covering the field of asymmetric reduction of prochiral substrates using oxazaborolidine catalysts have appeared in 1992 and 1993, respectively.[64]

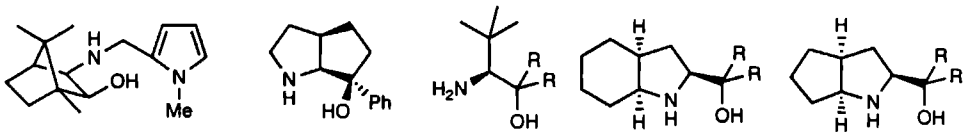


Scheme 2.6

The chiral oxazaborolidine catalyst complex consists of a boron hydride with various chiral ligands, based on amino acids derived vicinal amino alcohols in most cases. This survey covers chiral oxazaborolidines derived from the following amino alcohol precursors: (S)-α,α-dialkyl-2-aziridine-methanol (**17**),[65] (S)-α,α-dialkyl-2-azetidine-methanol (**18**),[66] (S)-α,α-dialkyl-2-pyrrolidine-methanol (**19**), (S)-α,α-dialkyl-2-piperidine-methanol (**20**),[67] (S)-α,α-dialkyl(indolin-2yl)-methanol (**21**),[68] (S)-α,α-dialkyl (1,2,3,4-tetrahydro-isoquinolin-3-yl)-methanol (**22**),[69] 2-hydroxy-3-(1-methyl-2-2-pyrrolyl) methyl-aminobornane (**23**),[70] (1S, 5R, 8S)-8-phenyl-2-aza-bicyclo-[3.3.0]octan-8-ol (**24**),[71] (S)-2-amino-3,3-dimethyl-1,1-dialkylbutane-1-ol (**25**),[72] 6,5 membered bicyclic catalyst (**26**),[73] and 5,5 membered bicyclic catalyst (**27**).[74]

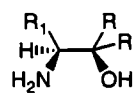


(S)-**17** (S)-**18** (S)-**19** (S)-**20** (S)-**21** (S)-**22**

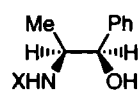


(S)-**23** (S)-**24** (S)-**25** (S)-**26** (S)-**27**

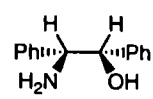
Many catalyst precursors **17-22**, **25-27** and **28-31** (*vide infra*) contain the diarylhydroxymethyl group as a structural unit, and numerous applications of this "magic" achiral functionality in chiral catalysts have been described.[75]



R_1 = Ph (**28**)
R_1 = CH_2Ph (**29**)
R_1 = $CH(Me)_2$ (**30**)
R_1 = $CH_2CH_2SR_2$ (**31**);
R_2 = Me, Et, i-Prop



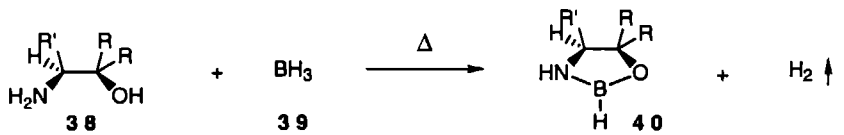
X = Me (**32**)
X = CH_2Ph (**33**)
X = CH_2Bu^t (**34**)
X = SO_2Ph (**35**)
X = SO_2Me (**36**)



(**37**)

More examples of acyclic amino alcohols (**25**) have been reported by several groups. In most cases amino alcohols derived from L-amino acids (**25**, **28-31**),[76] ephedrine derivatives (**32-36**),[77] and other chiral amino alcohols (**37**)[78] have been applied in the asymmetric reactions.

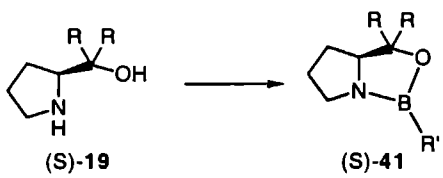
The general form of an oxazaborolidine complex (**40**) is a five-membered ring heterocycle, which is prepared from a borohydride (**39**) and aminoalcohol ligands (**38**) as depicted in Scheme 2.7. Recently, new procedures and reagents for the preparation of oxazaborolidines have been developed and amino alcohols are converted into the B-H, B-Me, B-phenyl, and B-Bu oxazaborolidine catalysts using borane,[79] trimethylboroxine, triphenyl-boroxine,[80] and butaneboronic acid,[81] respectively. Corey and coworkers developed the CBS process[82] which is an enantioselective oxazaborolidine catalyzed reduction using borane or catecholborane as stoichiometric reductant. On the bases of Itsuno's studies Corey introduced, isolated and identified chiral oxazaborolidines[83] derived from **19**. It was found that the oxazaborolidine prepared from **19** using trimethylboroxine (R = Ph, R' = CH_3) (**41b**) is more stable than the oxazaborolidines prepared from borane (BH_3-THF). Oxazaborolidine **41b** is not air and moisture sensitive as compared to catalyst **41a**. Furthermore, the reduction with this catalyst proceeds generally with higher enantioselectivity than with **41a** (R = Ph, R' = H).[84] A large scale synthesis of **19** and the corresponding **41b** was developed in the Merck Sharp & Dohme Research Laboratories.[85]



Scheme 2.7

An alternative synthesis of **41b** introduced by Corey et al.[86] involves a new alkylboronic acid equivalent in order to speed up the catalyst formation. Bis(trifluoroethyl)-alkyl boronates are outstanding reagents for oxazaborolidine formation: **41b** can be prepared in 30 min (110°C, 0.07 Torr) compared to 3-10 h with an alkyl boronic acid and 48 h for the reaction with BH_3-THF

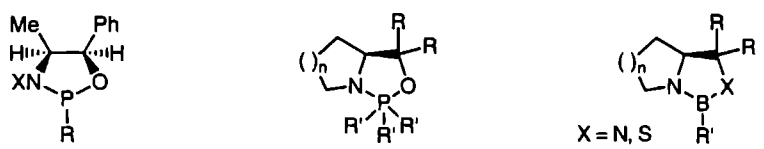
Chiral oxazaborolidine **41b** was used as a reducing agent in the synthesis of prostanoids,[87] trans-2,5-diarylfurans, oxiranes,[88] ginkgolides A and B,[89] forskolin,[90] bilobalide,[91] and fluoxetine,[92] some of which are important therapeutic agents.



41a: R = Ph, R' = H
41b: R = Ph, R' = CH_3
41c: R = Ph, R' = n-Bu
41d: R = β-naphtyl, R' = H
41e: R = β-naphty, R' = CH_3
41f: R = β-naphty, R' = n-Bu

Scheme 2.8

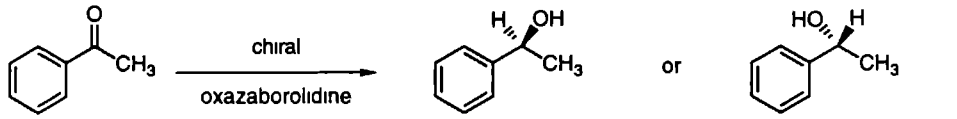
New types of catalysts for the reduction of ketoesters, enones and ketones have been described. Some examples of diazaborolidines **44** (X=N)[93] and oxazaphospholidine catalysts[94] **42-43** have been reported. In order to enable easy recovery and reuse of the chiral ligands and their borane complexes, the use of reagents attached to insoluble polymeric support is attractive.



Various polymer bound amino alcohols have been employed in oxazaborolidine catalyzed processes. It is interesting to note that in some cases the polymer bound reagent results in a higher enantioselectivity as compared to the same homogeneous reaction.[95] Recently, Itsuno and coworkers developed a polymer bound (S)-pyrrolidine-2-yl-methanol (**19**),[96] which was used in

asymmetric oxazaborolidine catalyzed reactions

Chiral 1,3,2 oxazaborolidines, either prepared *in situ* or isolated prior to use, have been used as catalysts in enantioselective reductions Acetophenone was tested as the model substrate in almost every case (Scheme 2 9) and the results are collected in Table 2 1 With the most commonly used oxazaborolidine **41** as the reference catalyst the data in this table reveal that high enantioselectivities (e e >90%) are obtained with the oxazaborolidines derived from aziridine-2-diphenyl methanol (**17**), azetidine-2-diphenylmethanol (**18**), the tricyclic oxazaborolidine derived from **24**, and the (S)-α,α-diphenyl(indolin-2yl)-methanol (**21**).



Acetophenone (**14**) (R)-1-phenylethanol (**15a**) (S)-1-phenylethanol (**15b**)

Scheme 2 9

The six membered ring analogue **20** is less efficient A remarkable reversal of the enantiofacial selectivity in the asymmetric reduction of ketones was observed when the oxazaborolidine derived from β-amino alcohol **21** and **26** were used (entries 7 and 13)

Table 2.1 Enantioselective reduction of acetophenone to 1-phenylethanol in the presence of various oxazaborolidines in THF

Entry	Amino alcohol	Catalyst [mol %]	reductant [mol %]	reaction time	T(°C)	Yield (%)	e e (%)	ref
1	(S)-**17**	R=Ph, R'=H, 10	110	5 min	30	95	94 (R)	97
2	(R)-**18**	R=Ph, R'=H, 10	60	5 min	0	90	95 (S)	98
3	(S)-**18**	R=Ph, R'=H, 10	90	5 min	30	90	98 (R)	99
4	(S)-**19**	R=Ph, R'=H, 10	100	1 min	25	92	97 (R)	100
5	(S)-**19**	R=Ph, R'=Me,10	100	1 min	25	99	97 (R)	101
6	(S)-**20**	R=Ph, R'=Me,10	60	5 min	0	90	87 (R)	102
7	(S)-**21**	R=Ph, R'=H, 2	100	60 min	30	93	93 (R)	103
8	(S)-**22**	R=Ph, R'=H, 10	100	10 min	25	91	51 (R)	104
9	(S)-**23**	R=Ph, R'=H, 5	70	10 min	25	92	73 (R)	105
10	(S)-**24**	R=Ph, R'=H, 10	60	5 min	30	95	97 (R)	106
11	(S)-**25**	R=Ph, R'=H, 10	100	5 min	25	91	89 (R)	107
12	(S)-**26**	R=H, R'=H, 10	100	10 min	25	95	90 (S)	108
13	(S)-**26**	R=Ph, R'=H, 10	100	10 min	25	96	49 (S)	E12
14	(R)-**27**	R=H, R'=H, 10[a]	100	30 min	95	90	33 (S)	109
15	(R)-**27**	R=Ph, R'=H, 1	100	10 min	25	91	61 (S)	110

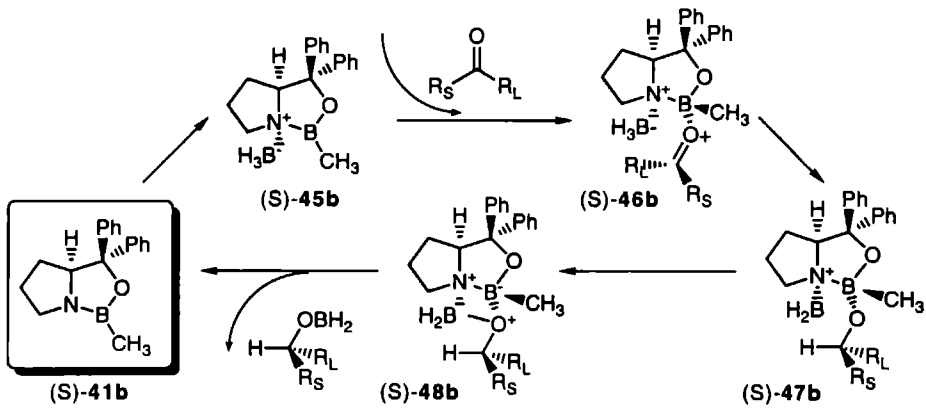
a) solvent = toluene

The same reversal of enantiofacial selectivity was observed when (S)-**26** with R=H was used, but with a much better enantioselectivity (e e =90%, entry 12) These results suggest that the structures of catalysts derived from **21** and **26** play an important role in controlling the asymmetric induction and is not only dependent on the stereochemistry of the chiral center of the catalyst

High enantioselectivities are obtained with most oxazaborolidines when aromatic ketones are used as substrates For aliphatic ketones the e e 's decrease considerably In order to obtain a high level of chiral discrimination between the diastereoselective transition states, apparently the presence of an aromatic moiety in the ketone is essential

The mechanism of the asymmetric reduction of prochiral ketones using oxazaborolidine catalysts has been proposed by Corey and Itsuno (Scheme 2 10) The first step in the catalytic cycle consists of a complexation of oxazaborolidine *e g* **41b** with a molecule BH_3-THF to form the reducing species **45b** *in situ* For (S)-**41a** this was verified on the bases of NMR studies,[111] moreover, the three dimensional structure of the borane adduct from **41b** has been determined by X-ray diffraction [112]

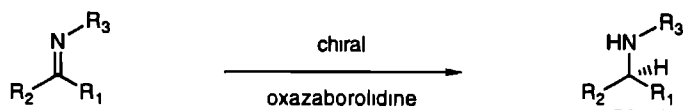
The Lewis acid base adduct **45b** of the boron of the oxazaborolidine moiety coordinates with the prochiral ketone in a *cis* configuration to the BH_3 molecule In **46b** an intramolecular hydride transfer from the BH_3 moiety on the *re*-face of the carbonyl substrate takes place via a six membered ring transition state yielding the (R)-alcohol Subsequent ligand exchange to form the alkoxy borane followed by displacement completes the reaction cycle



Scheme 2 10

Some details such as the role of the solvent have been clarified using computational methods [113] With *ab initio* molecular orbital methods, energies of formation and structural parameters of some analogous model systems and reactive intermediates of the oxazaborolidine catalysts could be obtained This provided further support for the proposed mechanism.

The reduction needs borane (BH_3-THF, BH_3-$S(Me)_2$, or catecholborane) as a source of hydrogen When the reaction is performed with additional equivalents of borane, the enantiomeric excess is only lowered marginally This implies that the rate of reduction with the complexed catalyst is considerably faster than with free borane



$R_1 = CH_3$, R_2 = Ph, R_3 = Ph (**49a**)
$R_1 = CH_3$, $R_2 = n\text{-}C_5H_{11}$, R_3 = Ph (**49b**)

Scheme 2 11

Neither borane (stoichiometric reductant) nor the oxazaborolidine catalyst reduce ketones, but in combination they form a complex which reduces ketones rapidly and gives the (S)- or (R)-alcohol in high chemical yields and high enantiopurities [114] This phenomenon is called "ligand acceleration"[115] and has been observed in other asymmetric reactions as well.[116] The enantioselective reduction of imines to the corresponding amines has received scarce attention and until now limited success has been achieved In 1985 Itsuno et al. reported the first effective enantioselective reduction of ketoxime ethers using the oxazaborolidine derived from (S)-valine

(**30**).[117] Cho and Chun accomplished the reduction of N-substituted ketimine derivatives in the presence of stoichiometric amounts of chiral oxazaborolidines derived from (S)-**30** and (S)-**19** using BH_3-THF as the reductant.[118]

A comparison study of the asymmetric reduction of the C=N double bond by chiral oxazaborolidines derived from (-) ephedrine (**32**), natural and unnatural α-amino acids, such as (S)-α,α-diphenyl-2-pyrrolidine-methanol (**19**), (S)-valine (**30**), a bicyclic proline (1R, 3R, 5R)-2-azabicyclo[3.3.0]octan-3-carboxylic acid (**27**), and (S)-tert-leucine (R = H, R = Ph) (**25**) using imine derivatives **49** was reported by Martens and coworkers in 1994[119] and the results are collected in Table 2.2. Both acetophenone N-phenylimine (**49a**) and 2-heptanone N-phenylimine (**49b**) were reduced to the corresponding amines **50a,b** in high yields (Scheme 2.11). In the reductions of **49a** all the selected chiral oxazaborolidines provided **50a** with good enantioselectivities. However, enantioselectivities for the aliphatic ketimine **49b** by **19-32** were low (5-18%).

Table 2.2 Enantioselective reduction of imines **49a** and **49b** in the presence of various oxazaborolidines.

R_1	R_2	R_3	Amino alcohol	reaction time[b]	Yield (%)	e.e.(%)	conf.
Me	Ph	Ph	(S)-**32**	8 h	96	79 (38)[c]	(R)
Me	Ph	Ph	(S)-**19**	3 h	98	78 (37)[c]	(R)
Me	Ph	Ph	(S)-**27**	2 h	96	9	(S)
Me	Ph	Ph	(S)-**30**	3 h	97	73	(R)
Me	Ph	Ph	(S)-**25a**	8 h	94	78	(R)
Me	Ph	Ph	(S)-**25b**	2 h	97	67	(R)
Me	n-C_5H_{11}	Ph	(S)-**32**	8 h	95	13	(R)
Me	n-C_5H_{11}	Ph	(S)-**19**	4 h	91	11	(R)
Me	n-C_5H_{11}	Ph	(S)-**27**	8 h	97	8	(S)
Me	n-C_5H_{11}	Ph	(S)-**30**	8 h	90	18	(R)
Me	n-C_5H_{11}	Ph	(S)-**25a**	24 h	87	5	(R)
Me	n-C_5H_{11}	Ph	(S)-**25b**	4 h	97	10	(R)

a) Imine : catalyst : borane-THF = (1 : 1.1 :1.1). b) solvent = THF. c) [catalyst.] = 10 mol %.

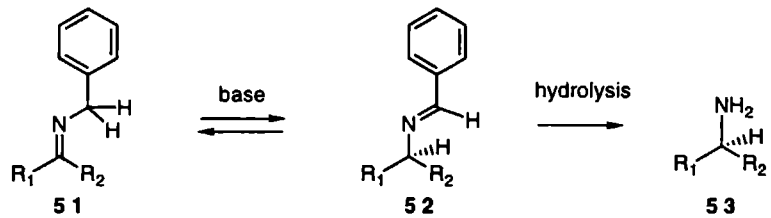
Chiral oxazaborolidines can also be applied as catalysts in asymmetric processes like Diels-Alder cycloadditions, 1,3-dipolar cycloadditions, hydroborations and additions of diethyl zinc to aldehydes. This wide scope in applications of the oxazaborolidine catalysts will provide a rich future for this relatively new class of chiral heterocycles. If the problems with the stability of the oxazaborolidines can be solved, these catalysts may be applied in industrial processes as well. An important drawback of the oxazaborolidine catalyzed asymmetric reductions as described in this overview are the safety aspects of large scale use of boranes.

An important new development involves the use of polymer bound catalysts, which have an advantage over free catalyst systems especially if recycling of the chiral catalysts is concerned. Polymer bound oxazaborolidine catalysts have been reported by several groups and may provide a useful methodology in catalytic asymmetric synthesis of chiral molecules in the future.

Part B Imine isomerization reaction

The second part of this thesis (chapters 5-7) deals with the synthesis of chiral amines from prochiral imines. The method is based on a double bond migration of a prochiral imine **51** yielding a chiral product imine **52** as depicted in Scheme 2.12. After hydrolysis of imine **52** the chiral amine **53** can be obtained. This imine isomerization reaction is base catalyzed and was described for the first time by Ingold and coworkers in 1933.

The main goal of the research presented in this thesis was the development of an asymmetric imine isomerization process using chiral bases. The results are described in chapter 6.

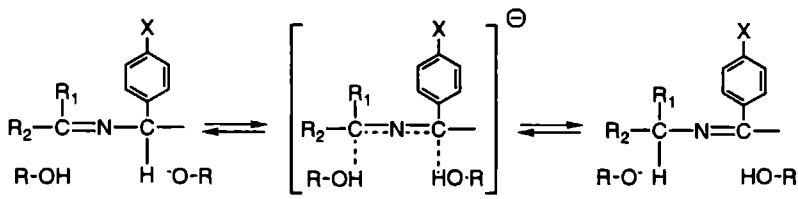


Scheme 2.12

2.6 Mechanism of the imine isomerization reaction

Two mechanisms for the imine isomerization reaction have been proposed. One involves a concerted mechanism without concrete intermediates (Scheme 2.13), and was postulated by Ingold and Ossorio in the 1930s and 1950s, respectively, whilst the other one is a two stage reaction with an aza-allyl anion intermediate (Scheme 2.14), as was proposed by Cram and coworkers in the 1960-70s.

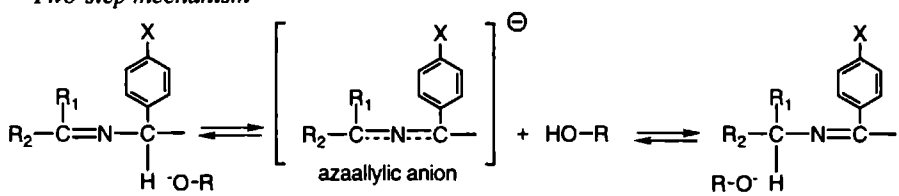
Concerted mechanism



Scheme 2.13

The evidence for a concerted mechanism of isomerization was based on a comparison of the rate constants of the imine isomerization of **54** to **61** catalyzed by ethoxide anions in deuterated ethanol or mixtures of deuterated ethanol and dioxane (Scheme 2.15).

Two-step mechanism



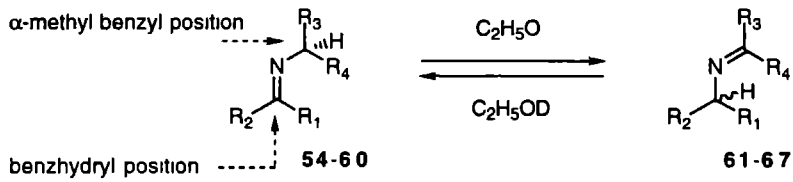
Scheme 2.14

The rate constants that could be determined in this process were k_i (the initial rate constant for isomerization), k_e (the initial rate constant for the introduction of deuterium) and k_α (the rate

constant for the loss of optical activity) The observation that these rate constants are about equal was taken as evidence for the absence of an aza-allyl anion intermediate during the isomerization, and a concerted mechanism for the proton transfer was proposed

Several model imines were examined in this imine isomerization reaction[120] and some typical examples are shown in Scheme 2 15 For the isomerization of imines **54** into **61** and **55** into **62** it was found[121] that $k_t = k_\alpha$ and for the isomerization of imine **56** into **63** all rate constants were equal ($k_t = k_e = k_\alpha$) DeSalas and Wilson already questioned[122] the one-step mechanism in 1938 as a result of their study of the reverse reaction of **57** into **64** using sodium ethoxide in deuterated ethanol They found that the rate of isotopic exchange of **64** exceeded the rate of isomerization and these results were inconsistent with the concerted mechanism

However, a study of Ossorio and Hughes[123] in 1952 on the isomerization of imine **57** to **64** revealed that for low conversions the racemization and isotopic exchange rates of the system as a whole were equal On the basis of this equality of rates the one-step mechanism was accepted



Entry	Imine system	R_1	R_2	R_3	R_4	Ref
1	**54 <=> 61**	C_6H_5	*p*-ClC_6H_4	CH_3	C_6H_5	124
2	**55 <=> 62**	C_6H_5	C_6H_5	CH_3	C_6H_5	see E1
3	**56 <=> 63**	C_6H_5	C_6H_5	H	*p*-$C_6H_5C_6H_4$	125
4	**57 <=> 64**	C_6H_5	H	H	*p*-$MeOC_6H_4$	126
5	**58 <=> 65**	*p*-ClC_6H_4	*p*-ClC_6H_4	C_6H_5	CH_3	127
6	**59 <=> 66**	H	$(Me)_3C$	C_6H_5	CH_3	128
7	**60 <=> 67**	Me	$(Me)_3C$	C_6H_5	CH_3	129
8	**61 <=> 68**	CO_2Et	$(Me)_3C$	C_6H_4N	CH_3	130

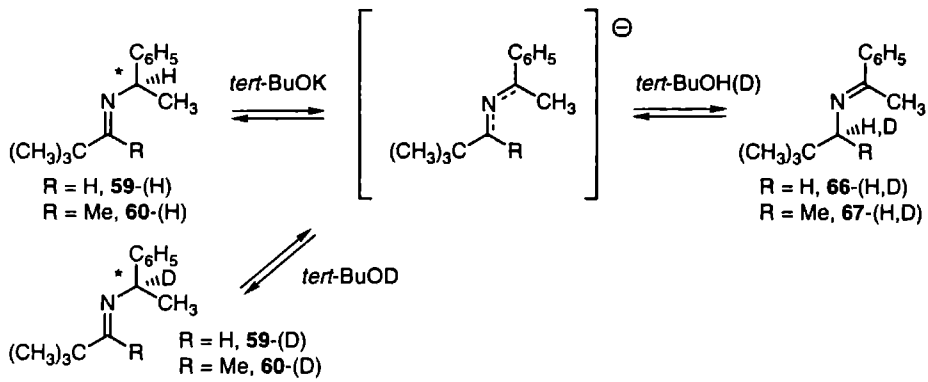
Scheme 2 15

A re-examination of the imine isomerization by Cram and coworkers in 1966 showed that carbanions do occur as intermediates in the isomerization of imines For this study imine system **58 <=> 65** was chosen, because of its structural similarity to the imine modelsystems **54<=>61** and **55<=>62** as analyzed by Ingold et al in the 1930s After 8% isomerization of optically active **58** to **65** in dioxane-deuterated ethylene glycol (1 1) using potassium ethylene glycoxide as the base, the recovered starting material had undergone almost no racemization and no isotopic exchange had occurred From these observations it was concluded that for the isomerization reaction of imine **58** to **65** the reaction constants k_e and k_α had equal values ($k_e = k_\alpha$) and these results are a confirmation of the observations made by Ingold and coworkers for the behavior of imines **54<=>61** and **56<=>63**

In order to obtain additional information, the relative rates of the reverse imine isomerization reaction of **65** to **58** and the deuterium incorporation into **65** under identical reaction conditions as had been used for the conversion of **58** into **65** were examined When **65** was allowed to isomerize for 10% to **58**, the recovered starting material **65** had undergone >95% isotopic exchange at the *benzhydryl* position (*vide supra*) The deuterium incorporation was much faster than isomerization ($k_t << k_e$), and in order to explain this result, a two step mechanism with aza-allyl anions as the essential intermediates was proposed by Cram [131] According to the law of microscopic reversibility, the imine isomerization reaction of **58** into **65** follows the same reaction

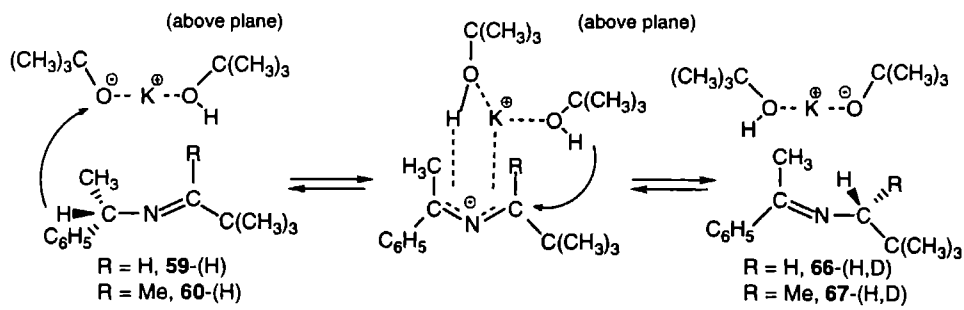
path as the reverse isomerization of **65** into **58** The fact that $k_l = k_\alpha$ in the isomerization of **58** to **65**, can be explained by assuming that protonation of the aza-allyl anion intermediate occurs exclusively at the *benzhydryl* rather than at the *α-methylbenzyl* position

Compound **58** structurally resembles **54** and **55**, and dioxane/ethylene glycol-glycoxide solvent-base mixture as used by Cram and coworkers is similar to dioxane/ethanol-ethoxide mixture applied by Ingold Therefore, it was concluded by Cram that carbanions occur as intermediates in the conversions of **54** into **61** and **55** into **62** and that the observed equalities of k_l and k_α, and k_l, k_e, and k_α as observed by Ingold, reflect a carbanion collapse that strongly favors the imine product as was found for the imine isomerization of **58**<=>**65**



Scheme 2 16

Other imine modelsystems **59** and **60** were designed by Cram et al , in which an unsymmetrical aza-allylanion is used with one benzylic and one non-benzylic position [132] When optically active **59** (R=H) was allowed to proceed to 17% isomerization using potassium *tert*-butoxide in deuterated *tert*-butyl alcohol, it was found that the recovered starting material had undergone an isotopic exchange of 57% and a racemization of only 3% The isomerized product **66** (R=H) had undergone 62% exchange of one atom of hydrogen for deuterium in the methylene position For imine modelsystem **60** the K-OtBu catalyzed isomerization to **67** was essentially stereospecific and the isolated imine **67** was enantiopure



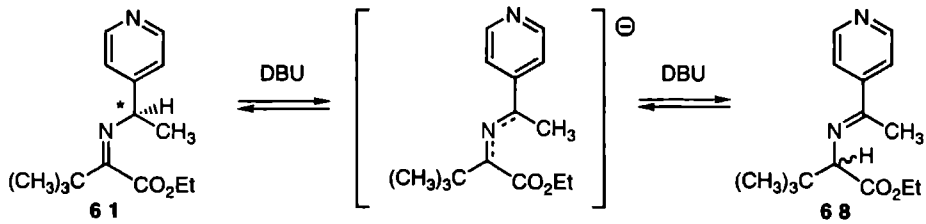
Scheme 2 17

The stereospecific isomerization of **59** into **66** and **60** into **67** in *tert*-butyl alcohol can be explained as follows By abstraction of the benzylic proton of **59** and **60** by potassium *tert*-butoxide, a contact ion pair is obtained, which is solvated by *tert*-butyl alcohol and ion paired with a potassium ion only on the face of which the proton was abstracted (above the plane of paper) Aza-allyl anion protonation to the tautomeric imine occurs within this asymmetrically ion paired anion yielding **66** and **67** in a stereospecific fashion The low dielectric constant of *tert*-butyl

alcohol probably results in potassium *tert*-butoxide-imine complex as a tight ion pair and the stereochemistry is retained by cation coordination at one face of the aza-allyl anion.

The effect of the addition of crown ethers during the isomerization reaction was monitored in order to obtain extra evidence for this 'ion-pair' hypothesis. In the presence of crown ethers a large decrease in the stereoselectivity of the potassium *tert*-butoxide catalyzed isomerization reaction was observed. Since crown ethers are known to effectively fill coordination sites of the potassium ion,[133] the contact ion pairs as described above are converted into crown ether separated ion pairs. It was concluded that the stereoselectivity of the imine isomerization is dependent on the asymmetric ion pairing with the potassium ion and that crown ethers effectively remove potassium away from the reaction site.

An imine model system that closely resembles that of the imines involved in a biological transamination is shown in Scheme 2.18.[134]

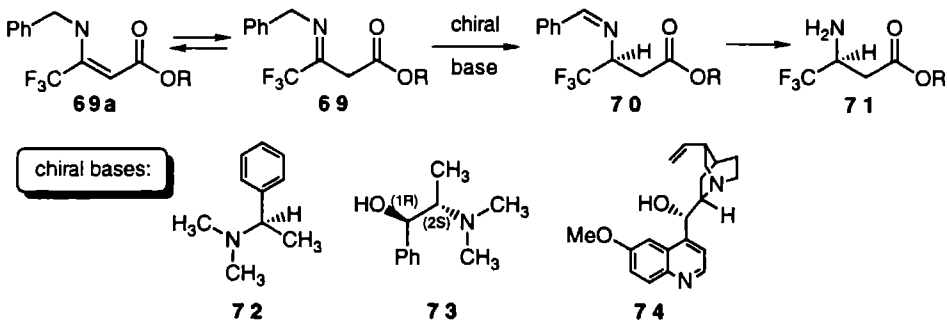


Scheme 2.18

In *tert*-butyl alcohol the equilibrium in the DBU catalyzed isomerization reaction of **61** into **68** lies on the side of the product imine **68**. (K_{eq} >199). The isomerization of **61** into **68** and racemization of **68** occurred at comparable rates. With the use of a kinetic model which corrected for racemization of the starting material **61** during the isomerization reaction, a stereoselectivity of 12% was found in the isomerization reaction of **61** into **68**. When pyridine and DMSO were applied as solvents stereoselectivities of 24% and 29% were obtained, respectively.

2.7 Catalytic asymmetric imine isomerization reaction

Sofar scarce attention has been paid to the asymmetric catalytic version of the imine isomerization reaction, in spite of the many publications about the isomerization of imines using achiral bases (section 2.6).



Scheme 2.19

Recently, the asymmetric [1,3]-proton shift imine isomerization catalyzed by chiral bases was described for the first time by Soloshonok et al.[135] and our group.[136] Soloshonok and coworkers described the catalytic asymmetric synthesis of β-fluoroalkyl-β-amino acids **71** via an imine isomerization reaction. During the reaction a prochiral β-imino-ester **69** was isomerized

using catalytic amounts (9-13 mol %) of commercially available (R)-(+)-N,N-dimethyl-1-phenyl ethylamine (**72**), (1R,2S)-(-)-N-methylephedrine (**73**) and (-)-cinchonidine (**74**) with moderate enantioselectivities (16-36%) as depicted in Scheme 2 19 The reactions were performed in the absence of solvents in the presence of catalysts **72-74** at 100°C for 26-65 h. The tertiary amine unit in the chiral bases was able to deprotonate the prochiral enamine-imine substrates **69a-69** under the reaction conditions applied

Another strategy in the catalytic asymmetric imine isomerization, based on the work of Cram and coworkers, was followed in the present study Instead of using achiral potassium alkoxide bases, the use of chiral potassium alkoxide bases, derived from their corresponding amino alcohols, was suggested The imine modelsystems **75** and **76** are derived from prochiral ketones (benzylacetone and acetophenone) and *p*-substitued-benzylamines (Figure 2 4) The results of the asymmetric catalytic imine isomerization experiments are described in chapter 6

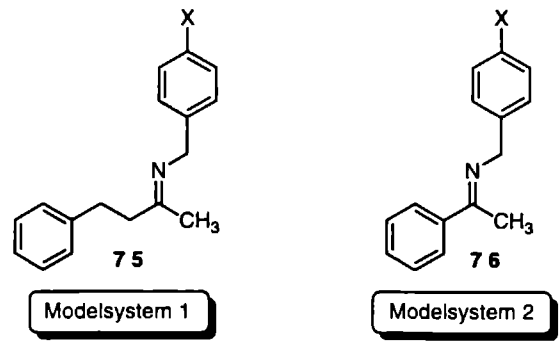
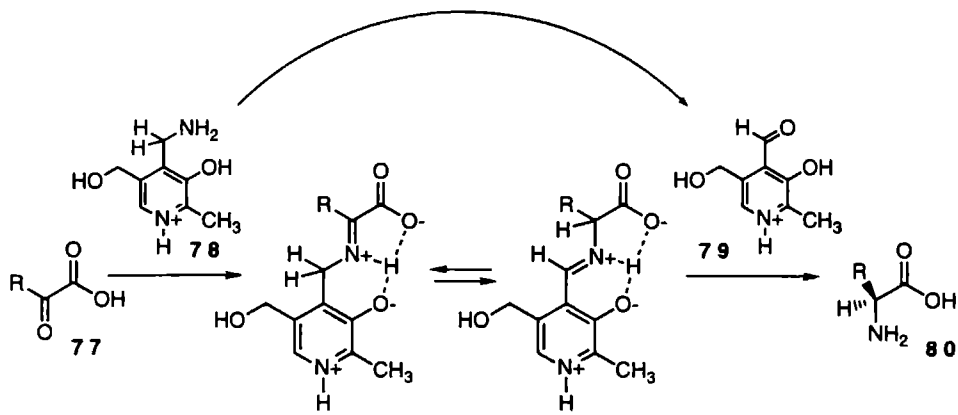


Figure 2 4

The biological counterpart of the asymmetric imine isomerization reaction is the transamination reaction,[137] which involves the base-catalyzed isomerization of intermediate imines derived from α-keto acids **77** and pyridoxamine (**78**) as well as from pyridoxal (vitamin B_6) (**79**) and α-amino acids **80**,[138] as depicted in Scheme 2.20 In biological systems vitamin B_6 is an essential cofactor for a large number of enzymes catalyzing various transformations of amino acids



Scheme 2 20

These reactions often proceed by formation of a Schiff base between the pyridoxamine and the α-keto acid, followed by a double bond migration and a proton shift. One of the reactions which is catalyzed by vitamin B_6 is the transamination reaction (Scheme 2.20) The key step in the

transamination reaction is an [1,3]-proton shift.[139] The isomerization is stereospecific, and in some enzymes containing a phosphate ester of pyridoxal, the proton transfer in this transamination occurs in an intramolecular fashion.

Asymmetric catalytic reactions mimicking biomolecular processes receive much current interest Recently, several examples of biomimetic systems based on supramolecular bilayer membranes have been described by Kikuchi et al [140] Here the catalytic functions exerted by naturally occurring vitamin B_6-dependent enzymes were mimicked using artificial supramolecules composed of a bilayer forming peptide lipid, a hydrophobic vitamin B_6 derivative and metal ions With the use of these supramolecular bilayer membranes an efficient isomerization reaction occurred, showing both high enantioselectivity and turnover behavior.

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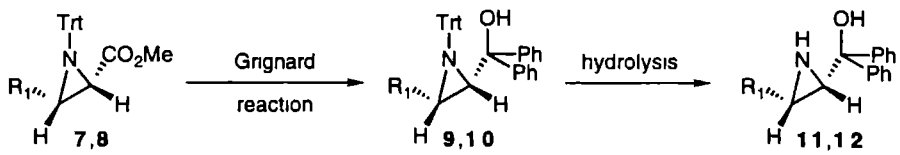
Synthesis and Crystal Structure of Enantiopure N-Trityl-Aziridine-2-Carbinols from L-Serine and L-Threonine

3.1 Introduction

The last two decades the synthesis of enantiomerically pure compounds forms an important issue in organic chemistry and much attention is devoted to the application of naturally occurring enantiopure starting materials in the synthesis of chiral compounds. In this respect chiral aziridines and chiral aziridine-2-carboxylic esters form an attractive class of compounds, since they are available in enantiopure form starting from natural compounds by various routes.[1] Using enantiopure aziridines and aziridine-2-carboxylic esters a wide range of chiral compounds such as anomalous α-amino acids,[2] antibiotics[3] and selective enzyme inhibitors[4] can be prepared.

Another strategy to obtain chiral compounds is the asymmetric conversion of prochiral substrates employing chiral catalysts. Recently, aziridines and derivatives thereof have been applied as new synthetic chiral catalysts in several asymmetric reactions [5] This chapter deals with the synthesis of new potential chiral catalysts derived from simple aziridine-2-carboxylic esters The actual application in asymmetric reactions will be described in chapters 4 and 6

Our interest in chiral small-ring heterocycles, especially functionalized epoxides,[6] and aziridines,[7] was a reason to investigate derivatives of aziridine-2-carboxylic esters **7** and **8** as new chiral catalysts in asymmetric reactions *N*-Trityl-aziridine-2-tertiairy alcohols **9** and **10**, and the corresponding detritylated aziridine-carbinols **11** and **12** (Scheme 3.1), were prepared and applied as catalysts in asymmetric imine isomerization reactions (chapter 6),[5b] and asymmetric reduction reactions (chapter 4),[5c] respectively.



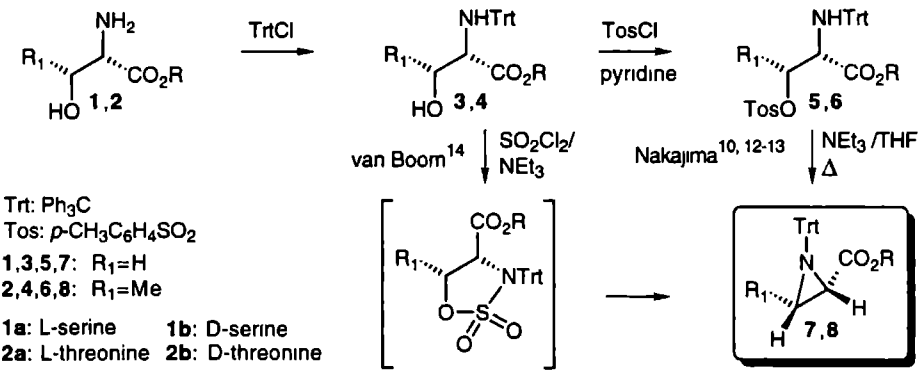
7,9,11: R_1=H, from L-serine
8,10,12: R_1=Me, from L-threonine

Scheme 3.1

A variety of routes to chiral nonracemic aziridine-2-carboxylic acid derivatives have been reported,[8] most of which rely either on the availability of enantiomerically pure starting materials from natural sources or on asymmetric transformations of C=C or C=N double bonds The ring closure of 1,2-amino alcohols or suitable derivatives thereof[9] provides a convenient and efficient synthesis of aziridines and aziridine-2-carboxylic esters. In this context amino acids are widely used as chiral starting materials. A general method for the synthesis of enantiopure *N*-unsubstituted aziridine-2-carboxylic esters from the corresponding oxirane-2-carboxylic esters in a two step

procedure was described by Legters et al.[7a,c] For the purpose of the study described in this chapter the readily available amino acids serine (**1**) and threonine (**2**) were selected as the starting material.

In 1972, the synthesis of *N*-substituted aziridine-2-carboxylic esters was reported by Nakajima and coworkers.[10] These authors make use of a modified Wenker[11] aziridine synthesis starting from serine (**1**) and threonine (**2**) (Scheme 3.2). In the first step the hydroxy group in *N*-tritylated α-amino-acid esters **3** and **4** was converted into the corresponding tosylate in pyridine as the solvent. The second step was performed using triethylamine as the base, which resulted in an intramolecular cyclization reaction[12] to give the *N*-trityl-aziridine-2-carboxylic esters **7** and **8**, as depicted in Scheme 3.2. In a subsequent report[13] Nakajima et al. replaced tosyl chloride by mesyl chloride.



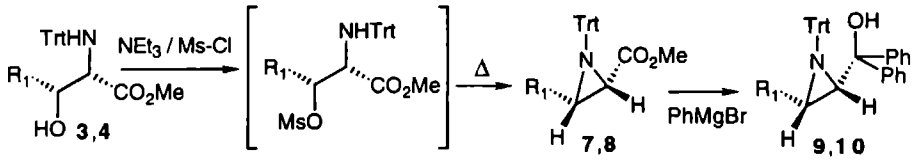
Scheme 3.2

Van Boom et al.[14] described a 2 mmol 'one-pot one step' procedure for the conversion of *N*-trityl-L-serine **3** and L-threonine esters **4** into the corresponding *N*-trityl-aziridine-2-carboxylic esters **7** and **8**, respectively, using sulfuryl chloride and an excess of triethylamine, as shown in Scheme 3.2. Korn et al.[15] applied the procedure for the synthesis of aziridines as described by van Boom et al. on a 100 g scale. It was found that during this multigram operation a by-product, *viz.* *N*-trityl-β-chloro-alanine benzyl ester, was formed in ca. 30% yield, arising from an aziridine ring opening by chloride ions. Separation of the desired *N*-trityl-aziridine-2-carboxylic esters (**7** and **8**) and the by-product turned out to be a laborious process involving column chromatography, followed by crystallization. In another study Korn and coworkers[16] compared the efficiency of the one-step preparation of enantiopure *N*-trityl-aziridine-2-carboxylic esters as described by van Boom et al.[14] with that originally proposed by Nakajima.[10, 12-13] Both procedures (Scheme 3.2) led to the desired aziridine compound in nearly identical yields (50-60%). X-ray diffraction analysis of methyl (-)-(2S)-*N*-trityl-2-aziridinecarboxylate was performed by Mishnev et al.[17] in 1983 and of benzyl (-)-(2S)-*N*-trityl-2-aziridinecarboxylate by Korn et al.[18] in 1993.

3.2 Results and Discussion

The aziridine-2-carboxylic esters **7** and **8** were used for the preparation of *N*-trityl-2-tertiairy alcohols **9** and **10** and the corresponding detritylated aziridine carbinols **11** and **12** (Scheme 3.1). It was important to have access to a convenient multigram scale synthesis of *N*-trityl-aziridine esters **7** and **8**, the precursors of **9**-**12**. The literature reports on this synthesis indicated (*vide supra*) that improvements were needed. To this end, a convenient multigram 'one-pot procedure' for the preparation of **7** and **8** from the corresponding *N*-trityl amino esters **3** and **4** was developed (Scheme 3.3). The desired conversion was performed in THF using 2.1 equivalents of triethylamine and 1.01 equivalents of mesyl chloride at reflux temperature[18] for 48 h. Product **7** was isolated in an almost quantitative yield with a purity of at least 95% according to GLC and

NMR, and was used as such in further reactions. After recrystallization from MeOH/NEt_3 the optical rotation of **7** (R_1=H), $[\alpha]^{20}_D$= -96.8° (c=1.1, MeOH), was in good agreement with the reported value[19] $[\alpha]^{20}_D$= -95.4° (c=1.1, MeOH) for this aziridine derivative. This method was also successfully applied for the synthesis of methyl (2S,3S)-1-trityl-3-methyl-2-aziridinecarboxylate (**8**, R_1=Me) from L-threonine. The optical rotation of **8**, $[\alpha]^{20}_D$= -97.1° (c=1, $CHCl_3$), has the same value but opposite sign as reported,[20] $[\alpha]^{20}_D$= +98.0° (c=1, $CHCl_3$), for the aziridine derived from D-threonine.



Trt: Ph_3C
Ms: CH_3SO_2

3,7,9: R_1=H, from L-serine
4,8,10: R_1=Me, from L-threonine

Scheme 3.3

The essential difference of the procedure described here and those reported previously is that the mesylation of the hydroxyl group as well as the aziridine ring closure can be carried out in one step on a multi-gram scale.

The *N*-trityl-aziridine-2-carboxylic esters **7** and **8** were converted into the corresponding *N*-trityl-aziridine-2-carbinols **9** and **10** using a Grignard reaction with 4 equivalents of phenylmagnesium bromide in ether or THF at room temperature for 2 h (Scheme 3.1). After purification of the crude products by chromatography, followed by crystallization from hexane/ether, the *N*-trityl aziridine-2-carbinols **9** and **10** were isolated in good yields (70%). The optical rotations of **9**, $[\alpha]^{20}_D$= -78.8° (c=1, $CHCl_3$), and **10**, $[\alpha]^{20}_D$= +22.5° (c=1, $CHCl_3$) have opposite signs, although the configuration at carbon C2 of the aziridine ring is (S) in both cases. The e.e.'s of the protected aziridine-2-tertiary alcohols **9** and **10** were determined by HPLC analysis using a chiral column (Chiralcel OD) and were higher than 99%.

The *N*-trityl-aziridine-2-yl-diphenyl carbinols **9** and **10** were further characterized by X-ray diffraction analysis and NMR. Large cubic-shaped colorless and transparent crystals of **9** and **10** were obtained by slow recrystallization from hexane/ether (2:1, v/v) solutions over a period of 64 h. X-ray analysis revealed that the crystals from **9** and **10** are orthorhombic and monoclinic, respectively. Orthorhombic crystals were also obtained for *N*-trityl-aziridine-2-carboxylic benzyl ester derived from L-serine as described by Korn and coworkers.[18] The X-ray structure analysis (see Figure 3.1) reveals that the *N*-trityl group is positioned *anti* to the carbinol in both **9** and **10**.

Comparison of the structure of **9** and **10** shows that the relative positions of the phenyl rings in the diphenylcarbinol unit are very similar in both compounds, whereas the orientation of the phenyl rings of the trityl groups are slightly different (Table 3.1). The dihedral angles between the phenyl rings of the diphenylcarbinol moiety and the aziridine ring are 94.0 and -142.6° in **9** and 93.0 and -146.2° in **10** (Table 3.1, entries 11-12). The dihedral angles between the aziridine ring and the phenyl rings of the trityl groups in **9** are -162.0, 84.7, and -40.1° and for aziridine carbinol **10** the values of the corresponding dihedral angles are -144.4, 101.5, and -18.3°, respectively (Table 3.1, entries 4-6). This difference in spatial orientation of the phenyl rings in the trityl groups is due to the presence of the *cis* methyl group in aziridine carbinol **10**. Inspection of space filling models of **9** and **10** confirms this observation. For the O-H group in the aziridine carbinols one can envisage an intramolecular hydrogen bonding with the nitrogen of the three-membered ring. It is of interest to determine the orientation of the OH group in these carbinols more precisely. From the X-ray it was deduced that indeed a hydrogen bond is present in the *N*-trityl carbinols **9** and **10**.

Table 3.1 Bond lengths, bond angles and dihedral angles of *N*-trityl aziridine diphenylcarbinols **9** and **10**

Entry	Bond length (Å)	9	10	Bond angle (°)	9	10	Dihedral angle (°)	9	10
1	N(1)-C(5)	1.497	1.505	C(3)-N(1)-C(5)	122.1	119.2	C(3)-N(1)-C(5)-C(10)	-88.36	-72.35
2							C(3)-N(1)-C(5)-C(20)	158.36	173.59
3							C(3)-N(1)-C(5)-C(30)	33.57	53.71
4				C(2)-N(1)-C(5)	123.4	121.9	C(2)-N(1)-C(5)-C(10)	-162.0	-144.40
5							C(2)-N(1)-C(5)-C(20)	84.7	101.54
6							C(2)-N(1)-C(5)-C(30)	-40.1	-18.33
7	N(1)-C(3)	1.458	1.475	C(2)-N(1)-C(3)	60.58	60.9	C(4)-C(2)-C(3)-N(1)	-99.5	-101.29
8				N(1)-C(2)-C(4)	113.6	115.6	C(4)-C(2)-N(1)-C(5)	-132.32	-133.38
9	C(3)-C(2)	1.472	1.488	C(3)-C(2)-C(4)	123.9	126.1	C(3)-C(2)-C(4)-C(40)	162.19	163.29
10				N(1)-C(3)-C(2)	59.81	59.1	C(3)-C(2)-C(4)-C(50)	-74.42	-75.89
11	N(1)-C(2)	1.460	1.461	N(1)-C(2)-C(4)	113.6	115.6	N(1)-C(2)-C(4)-C(40)	94.02	93.03
12							N(1)-C(2)-C(4)-C(50)	-142.6	-146.15
13	C(2)-C(4)	1.537	1.525	O(1)-C(4)-C(2)	108.3	109.4	H(1)-O(1)-C(4)-C(2)	21.05	25.18
14				C(2)-C(4)-C(50)	114.0	112.7	C(3)-C(2)-C(4)-C(50)	-74.42	-75.89
15				C(2)-C(4)-C(40)	107.6	108.8	C(3)-C(2)-C(4)-C(40)	162.19	163.29
16	C(4)-O(1)	1.429	1.431	C(4)-O(1)-H(1)	102.7	106.3	C(4)-O(1)-H(1)-N(1)	-12.32	-16.33
17	O(1)-H(1)	0.826	0.830						
18	N(1)-H(1)	2.013	2.140	N(1)-H(1)-O(1)	131.97	125.01			
19	N(1)-O(1)	2.638	2.702						

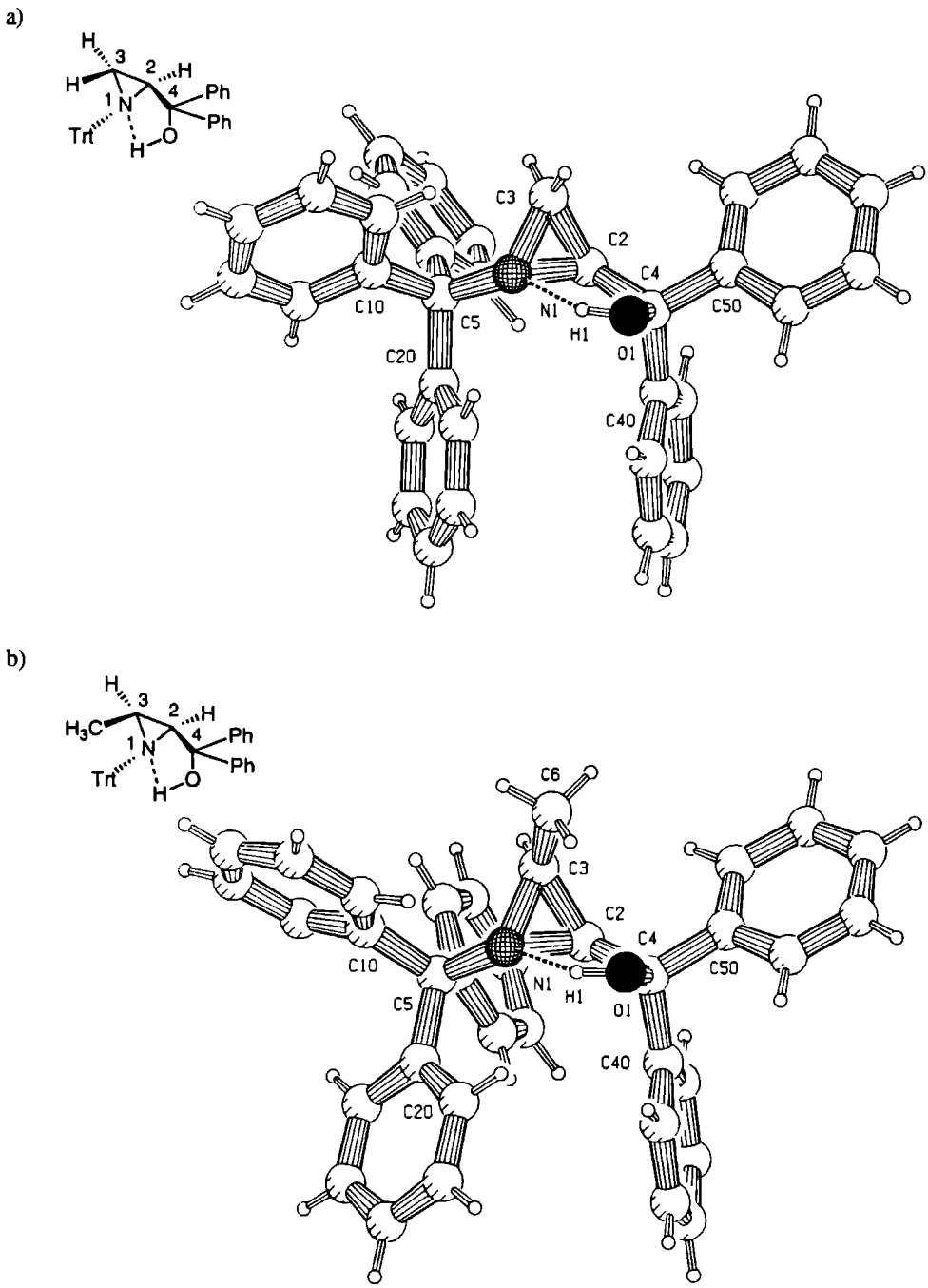


Figure 3.1 PLUTON drawings[27] of X-ray structures of *N*-trityl carbinols **9** (a) and **10** (b)

The N-H distances in **9** and **10** could be determined from the X-ray diffraction data and were 2.01 and 2.14 Å, respectively (Table 3.1, entry 18). These distances between the aziridine nitrogen

and the carbinol hydrogen atom are indicative of the presence of an intramolecular hydrogen bond in both aziridine carbinols as shown in Figure 3.1. The N-H-O bond angles in **9** and **10** amount to 131 97 and 125 01°, respectively (Table 3 1, entry 18), which is an average value for a hydrogen bond present in a five-membered ring structure

Evidence for the presence of a hydrogen bond in the molecules **9** and **10** in solution was also obtained from temperature dependent ^{1}H-NMR experiments in deuteriochloroform In the 400 MHz ^{1}H-NMR spectrum of carbinol **9**, measured at 298K, the OH hydrogen signal appears at 4 438 ppm When the temperature was raised to 315K this proton signal shifts upfield to 4.387 ppm ($\Delta\delta$ = 0 051 ppm), which is an indication of the presence of an intramolecular hydrogen bond at ambient temperature A similar behavior was observed for carbinol **10** When the temperature was raised from 298K to 315K the OH proton signal shifts from 4 919 to 4 858 ppm ($\Delta\delta$ = 0 061 ppm), implying that an intramolecular hydrogen bond is present at ambient temperature Saturation of the water signal present in the deuteriochloroform gave a reduction of the OH proton signal which is indicative of a fast exchange of the carbinol proton with water.

The results presented above show that the 'one-pot' synthesis of the enantiopure *N*-trityl aziridine esters **7** and **8** has been considerably improved in comparison with Nakajima's two step procedure[10, 12 13] and van Boom's 'one-step'-process [14] The X-ray analysis reveals that the relative positions of the phenyl rings in the diphenylcarbinol unit in **9** and **10** are very similar, whereas the orientation of the phenyl rings of the trityl groups are slightly different The X-ray analysis as well as ^{1}H-NMR measurements indicate that in carbinols **9** and **10** an intramolecular hydrogen bond is present in the crystalline state and in solution

3.3 Experimental Section

General Methods Optical rotations were determined with a Perkin Elmer automatic polarimeter, model 241 MC using 1% solutions at 20°C in the solvents indicated Melting points were determined using a Reichert thermopan microscope equipped with crossed polarizers, and are uncorrected GLC was conducted with a Hewlett-Packard HP 5890A and HP 5790A gas chromatograph, using a capillary column (25m) of HP-1 and PAS-1701, a temperature program from 100-250°C at 10°C/min, followed by 10 min at 250°C (isothermal), and nitrogen at 2 ml/min (0 5 atm) as the carrier gas The instruments were connected to a HP 3396 or HP 3390 calculating integrator The enantiomeric purity of aziridine carbinols **9** and **10** was determined by HPLC[21] using a chiral column with n-hexane/2-propanol (ratio as indicated) as the eluent The chromatographic system consisted of a Pharmacia LKB (Sweden) model 2150 HPLC pump, a LKB model 2152 HPLC controller and a Rheodyne injector The injection loop had a 20-µl capacity The column used was a Daicel Chiralcel OD (250*4 6 mm I D , 10 µm) from J T Baker (Deventer, The Netherlands) The flow rate was 1 0 ml/min and the column was operated at ambient temperature The column effluent was monitored with a LKB model 2138 uvicord S absorbance detector at 254 nm ^{1}H- and ^{13}C-NMR were performed on a Bruker AC 100 (100 MHz, FT) or a Bruker AM-400 (400 MHz, FT) spectrometer using solutions in $CDCl_3$ (internal Me_4Si) IR spectra were determined on a Perkin Elmer 298 spectrophotometer FT IR spectra were determined on a Biorad WIN IR FTS 25 spectrophotometer Elemental analyses were performed on a Carlo Erba Instruments CHNS-O EA 1108 element analyzer Electron impact (EI) and chemical ionization (CI) mass spectra, induced with methane gas at 200°C and emission current 0 5 mA, were determined on a VG 7070E spectrometer

Chemicals Diethyl ether was pre-dried over calcium chloride then distilled from calcium hydride Tetrahydrofuran was distilled from potassium/benzophenone under Schlenk conditions Benzene and absolute ethanol (both Merck p a quality) were used without further purification All other solvents were either P A or reinst" quality All other reagents are commercially available and were used as received Unless otherwise stated, yields refer to isolated yields of products of greater than 95% purity as estimated by capillary GC and / or ^{1}H NMR spectroscopy

(-)-(2S)-Methyl-1-trityl-2-aziridinecarboxylate (7, R_1=H)

Compound **3** (R_1=H) (93 8 g, 259 mmol) was dissolved in THF (700 mL) at room temperature Triethylamine (83 0 mL, 574 mmol, 2 2 equiv) was added, followed by gradual addition of mesyl chloride (20 0 mL, 262 mmol, 1 01 equiv) during a period of 15 min The mixture was left for 30 min at 20°C Then the temperature was raised to 66°C and the reaction mixture was heated at reflux for 48 h The reaction was monitored with capillary GLC After 48 h the reaction mixture was cooled to room temperature and concentrated Then 300 mL of ethyl acetate was added, followed by extraction with an aqueous citric acid solution (10%) (3x 100 mL) and a saturated sodium bicarbonate solution (3x 50 mL) The combined organic layers were dried ($MgSO_4$) and concentrated Yield 100% (92 0 g, 259 mmol)

Purity: 95% according to capillary GLC, TLC: R_f = 0.7 (CH_2Cl_2). For characterization 1 g of the almost pure material was recrystallized from MeOH/NEt_3 (50 mL/15 drops) yielding material with a purity of 99.5% according to GLC. The NEt_3 was added to prevent detritylation of the product during the purification procedure. $[\alpha]^{20}_D$ -86.2° (c=1, $CHCl_3$), $[\alpha]^{20}_D$ -96.8° (c=1.1, MeOH), m.p.: 127-129°C. Calc. for $C_{23}H_{21}O_2N$ (343.43): C 80.44, H 6.16, N 4 08 %, found C 80.11, H 6.23, N 4.07 %. ^1H NMR (100 MHz in $CDCl_3$): δ 7.55-7.21 (m, 15H, aromatic H, Trt); 3.76 (s, 3H, O$\underline{C}H_3$), 2.24 (dd, 1H, J = 1.6 and 2.7Hz, βCH, Azy); 1.89 (dd, 1H, J = 6.2 and 2.7Hz, αCH, Azy); 1 40 (dd, 1H, J = 1.6Hz and 6.2Hz, βCH, Azy) ppm. ^{13}C NMR (25 2 MHz in $CDCl_3$): δ 171 9 (C=O ester); 143 6-127.0 (aromatic C); 74.4 ($Ph_3\underline{C}$-N); 52.1 (O$\underline{C}H_3$ ester); 31.7 (αCH, Azy); 26.7 (βCH_2, Azy) ppm. IR (KBr): υ 3100-3000, 1600 (arom.), 3000 - 2900 (alkyl), 1740 (C=O) cm^{-1}.

(-)-(2S,3S)-Methyl-1-trityl-3-methyl-2-aziridinecarboxylate (8, R_1=Me)

Using the same procedure as described for **7**, compound **4** (R_1=Me) (23.4 g, 62.4 mmol) was converted into **8** in a quantitative manner (22.3 g, 62.4 mmol) with a purity >90% according to NMR The reaction was monitored using TLC, because the aziridine was not stable using capillary GLC. For characterization, 1 gram of the material thus obtained was recrystallized from MeOH/hexane yielding a clear crystalline compound. $[\alpha]^{20}_D$ -97.1° (c=1, $CHCl_3$), m p.: 112-113°C. Calc. for $C_{24}H_{23}O_2N$ (357.43): C 80.64, H 6.48, N 3 92 %, found C 80.56, H 6 42, N 3 96 %. ^1H NMR (100 MHz in $CDCl_3$): δ 7.58-7.10 (m, 15H, aromatic H, Trt); 3 74 (s, 3H, O$\underline{C}H_3$); 1.88 (d, 1H, J = 6 3Hz αCH, MeAzy), 1,69-1.56 (m, 1H, βCH, MeAzy); 1,36 (d, 3H, J = 5.2Hz, CH_3) ppm. ^{13}C NMR (25 2 MHz in $CDCl_3$): δ 170.7 (C=O ester); 143.9-126.7 (aromatic C); 75.1 ($Ph_3\underline{C}$-N), 51.8 (O$\underline{C}H_3$ ester); 35 9 (αCH, Azy); 34.6 (βCH, Azy); 13.4 (CH_3-Azy) ppm. IR (KBr). υ 3100-3000, 1600 (arom), 3000 - 2900 (alkyl), 1740 (C=O) cm^{-1}

For the Grignard reactions described below all glassware was dried at 140°C overnight, and flame dried under vacuum using a Schlenk apparatus The magnesium was activated by magnetic stirring overnight under an argon atmosphere.[22] All reactions were carried out under a static pressure of argon.

(-)-(2S)-1-Trityl-aziridin-2-yl-diphenylmethanol (9)

To a stirred suspension of magnesium turnings (2.52 g, 104 mmol, 3.4 equiv.) in ether (20 ml) was gradually added bromobenzene (10.8 ml, 103 mmol, 3.4 equiv.) in ether (15 mL). After heating the Grignard reagent for 1.5 h compound **7** (R_1=H) (10.3 g, 29.9 mmol) in THF (20 mL) was added dropwise over a period of 20 min The reaction was monitored with capillary GLC and TLC (CH_2Cl_2). After 1.5 h the reaction was quenched with a saturated $(NH_4)_2SO_4$ solution (30 mL) followed by the evaporation of the organic solvents. The residue was extracted with ether (3x 150 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated. Yield: 92% (12.9 g, 27.5 mmol) of a yellow crystalline compound. The crude product was purified by flash column chromatography (hexane/ethyl acetate 12 1) and NEt_3 (1 mL/L) was added to the eluens to prevent detritylation of the product during the purification procedure. Recrystallization from MeOH/NEt_3 (50mL/15 drops) afforded 8 7 g (62%) of **9**, m p .133.5-134.5°C. $[\alpha]^{20}_D$ -78.8° (c=1, $CHCl_3$). Calc. for $C_{34}H_{29}NO$ (467.61): C 87.33, H 6 25, N 3.00 %, found: C 87.22, H 6.26, N 2 96 % MS (EI) : m/e: 390 (M-$C_6H_5^+$, 0.5%); 243 (Trt^+, 100%), 165 (Trt-Ph^+, 53 5%), 183 (($(C_6H_5)_2C$-OH^+, 30 4%), 105 ($C_6H_5CO^+$, 32.0%); 91 ($C_7H_7^+$, 8.0%); 77 ($C_6H_5^+$, 25.6%). ^1H NMR (100 MHz in $CDCl_3$); δ 7.40-7.02 (m, 25H, aromatic H, Trt, Phenyl); 4.36 (s, 1H, OH); 2 29.(dd, 1H, J = 6 3 and 3.2Hz, αCH, Azy), 2.00 (d, 1H, J = 3 2Hz, βCH, Azy); 1.25 (d,1H, J = 6.3Hz, βCH, Azy) ppm. ^{13}C NMR (25 2 MHz in $CDCl_3$), δ 147 0-125 9 (aromatic C); 74.0 and 73.9 ($Ph_3\underline{C}N$ and COH alcohol); 41.5 (αCH, Azy), 23.6 (βCH, Azy) ppm. IR (KBr): υ = 3500-3300 (OH); 3100-3000, 1600 (aromatic) cm^{-1}.

(+)-(2S,3S)-1-Trityl-3-methyl-aziridin-2-yl-diphenylmethanol (10)

To a stirred suspension of magnesium turnings (1.49 g, 61.2 mmol, 4 equiv.) in THF (75 ml) was gradually added bromobenzene (6 5 ml, 61.2 mmol, 4 equiv.). After heating the Grignard reagent for 30 min compound **8** (R_1=Me) (5 47 g, 15.3 mmol) in THF (25 mL) was added dropwise over a period of 20 min The reaction was monitored with TLC (hexane/ethyl acetate = 3:1). After 1.5 h the reaction was quenched with a saturated NH_4Cl solution (50 mL). The crude reaction mixture was extracted with ether (3x 100 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated. The crude product was purified by flash column chromatography (hexane/ethyl acetate 3·1). Recrystallization from hexane/ether afforded 5.6 g (76%) of **10**, m.p ·174-175°C. $[\alpha]^{20}_D$ = +22.5° (c=1, $CHCl_3$). Calc. for $C_{35}H_{31}NO$ (481.637): C 87.28, H 6.49, N 2.91 %, found: C 87.31, H 6.68, N 2.96 %. MS (EI) m/e. 481 (M^+, 0.1%); 243 (Trt^+, 100%); 183 (($(Ph)_2C$-OH^+, 37.2%); 165 (Trt-Ph^+, 39 8%); 105 ($C_6H_5CO^+$, 23 5%), 91 ($C_7H_7^+$, 5%); 77 ($C_6H_5^+$, 14.1%). ^1H NMR (100 MHz in $CDCl_3$), δ 7.32-7.02 (m, 25H, aromatic H, Trt, Phenyl); 4.95 (s, 1H, OH); 2.22.(d, 1H, J = 6.3 Hz, αCH, Azy); 1.68 (m, 1H, βCH, Azy); 1 19 (d, 3H, J = 5.7Hz, CH_3) ppm. ^{13}C NMR (25.2 MHz in $CDCl_3$); δ 148.6-125.7 (aromatic C), 75.3 and 73.6 ($Ph_3\underline{C}N$ and COH alcohol), 45.3 (αCH, MeAzy); 32.0 (βCH, MeAzy) 13.7 (CH_3, Azy) ppm. IR (KBr): υ = 3500

-3300 (OH), 3100-3000, 1600 (aromatic); 3000-2900 (alkyl) cm^{-1}.

Structure analysis

Atomic coordinates, bond lengths and angles, and thermal parameters of **9** and **10** have been deposited with the Cambridge Crystallographic Data Centre.[23]

(-)-(2S)-1-Trityl-aziridin-2-yl-diphenylmethanol (9) A transparent and colorless crystal of dimension 0 25 x 0 42 x 0 54 mm was mounted in a glass fiber and the structure of the azirıdine carbinol **9** was determined at a temperature of 284 K. Crystal data are given in Table 3.1. The crystal structure was determined using CRUNCH95 [24] The structure was refined by full-matrix least-squares on F_o^2 values using SHELXL[25] with anisotropic parameters for the non-hydrogen atoms. The refinement converged to an R-value of 0.087 During the structure determination the configuration of the chiral aziridine carbon C2 was assumed to be 2S The hydrogen atoms of the phenyl rings were placed at calculated positions and were subsequently freely refined. All other hydrogen atoms were taken from a difference fourier map

Data collection and processing[26] for (9) CAD4 diffractometer, ω-mode with ω scan width = 1.5 degrees, ω scan speed 30 s ; graphite-monochromated $M_oK\alpha$ radiation, 29646 reflections measured (1 68 < Θ < 29 97), 7438 unique [merging R = 0.087 after absorption correction (max., min transmission factors = 0 986, 1.013)], giving 4228 with $I > 2\sigma(I)$. Crystal decay, *ca.* 1% correction during processing

(+)-(2S,3S)-1-Trityl-3-methyl-aziridin-2-yl-diphenylmethanol (10) A transparent and colorless crystal of dimension 0 21 x 0.39 x 0 46 mm was mounted in a glass fiber and the structure of the aziridine carbinol **10** was determined at a temperature of 208 K Crystal data are given in Table 3.1. The crystal structure was determined using CRUNCH95 [24] The structure was refined by full-matrix least-squares on F_o^2 values using SHELXL[25] with anisotropic parameters for the non-hydrogen atoms. The refinement converged to an R-value of 0 049 During the structure determination the configuration of the chiral aziridine carbons C2 and C3 were assumed to be 2S and 3S, respectively The hydrogen atoms of the phenyl rings were placed at calculated positions and were subsequently freely refined The hydrogen atoms of the methyl group were obtained by rotation of an idealized methyl group to match maximum electron density in a difference fourier synthesis. All other hydrogen atoms were taken from a difference fourier map.

Data collection and processing[26] for (10). CAD4 diffractometer, ω-mode with ω scan width = 1 5 degrees, ω scan speed 30 s., graphite-monochromated $M_oK\alpha$ radiation, 9452 reflections measured (1 60 < Θ < 24 97), 4727 unique [merging R = 0 049 after absorption correction (max., min transmission factors = 0.968, 1.026)], giving 3369 with $I > 2\sigma(I)$ Crystal decay, *ca* 3% correction during processing

Table 3.2 Crystallographic data for *N*-trityl aziridine carbinols **9** and **10**

	aziridine carbinol **9**	aziridine carbinol **10**
Empirical formula	$C_{34}H_{29}NO$	$C_{35}H_{31}NO$
Formula weight	467.58	481.61
Space group	$P2_12_12_1$	$P2_1$
a (Å)	8.2743(7)	10.565(2)
b (Å)	14.9630(11)	10.0123(11)
c (Å)	20.640(2)	12.8568(14)
Crystal system	Orthorhombic	Monoclinic
V (Å^3)	2555.3(3)	1348.2(3)
Z	4	2
D_x (g/cm^3)	1.215	1.186
λ	0.71073	0.71073
μ($M_oK\alpha$) (cm^{-1})	0.67	0.65
Temperature (K)	284	208
Radiation	$MoK\alpha$	$MoK\alpha$
R	0.087	0.049

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18) Note When the reaction was performed at 50°C in stead of reflux temperature, the *N*-trityl-aziridine-2-carboxylic ester and several reaction intermediates were formed according to GLC After 48 h of additional heating of the reaction mixture at reflux temperature the product could be isolated in quantitative yield
19) Reported value of methyl (2S)-1-trityl-2-aziridinecarboxylate $[\alpha]^{20}_D$= -95 4° (c=1 1, MeOH), see Nakajima, K , Tanaka, T , Neya, M , Okawa, K , *Bull Chem Soc Jpn* , **1982**, *55*, 3237
20) Reported value of methyl (2R,3R)-1-trityl-3-methyl-2-azirindinecarboxylate $[\alpha]^{20}_D$= +98 0° (c=1, $CHCl_3$), the optical antipode of the synthesized methyl (2S,3S)-1-trityl-3-methyl-2-azirindinecarboxylate, see ref 22
21) The HPLC analysis was performed on the aziridine carbinols **8** and **9** using a Daicel Chiralcel OD column (eluent hexane/2-propanol = 95 5, v/v)
22) Baker, K V , Brown, J M , Hughes, N , Skarnulis, A J , Sexton, A , *J Org Chem* , **1991**, *56*, 698
23) The atomic coordinates for **9** and **10** have been deposited with the Cambridge Crystallographic Data Centre The coordinates can be obtained, on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK The contents of this chapter have been submitted for publication Willems, J G H , Hersmis, M C , de Gelder, R , Smits, J M M , Hamminк, J B , Dommerholt, F J , Thijs, L , Zwanenburg, B , *J Chem. Soc , Perkin Trans 1*, (submitted for publication)
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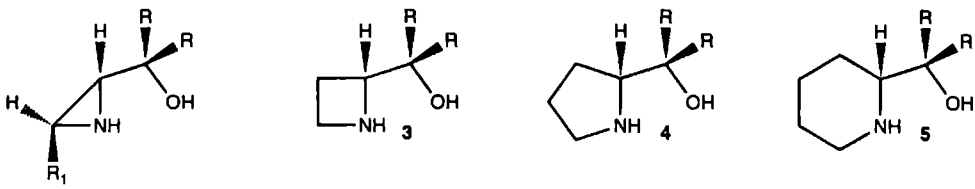
Chapter 4

Asymmetric Catalytic Reduction of Prochiral Ketones using Chiral Oxazaborolidines derived from Aziridine Carbinols

4.1 Introduction.

The development of asymmetric catalytic processes is a fast growing and interesting field in organic chemistry, stimulated by the general advantages of catalytic processes and the synthetic challenges for organic chemists A substantial part of this research has been directed towards the synthesis of chiral secondary alcohols by asymmetric reduction of prochiral ketones [1] The application of microbial processes,[2] heterogeneous metal catalysts[3] and the enantiocontrolled homogeneous catalytic reduction using chirally modified hydride reagents have been intensively investigated in recent years



1 R_1 = H from serine
2 R_1 = Me from threonine

One of the most important examples is the homogeneous catalytic hydrogenation of a wide range of functionalised ketones using chiral transition metal catalysts [4] Another successful reaction for the preparation of chiral alcohols is based on the use of 1,3,2-oxazaborolidines as chiral inductor in the reduction process Chiral 1,3,2-oxazaborolidines are generated from chiral 1,2-aminoalcohols and borane as was first reported by Itsuno and coworkers [5] Corey et al [6] soon thereafter prepared an oxazaborolidine derived from α,α-diphenyl-2-pyrrolidinemethanol (**4**) which was employed in the reduction of prochiral ketones with borane (BH_3-THF, CBS-method)

After the discovery of the mechanism of action of chiral oxazaborolidines in the catalytic enantioselective reduction of ketones in 1987 (the CBS reduction)[7] the number of applications of chiral oxazaborolidine derivatives is still growing Modifications of the original CBS method with respect to the method of preparation,[8] structure of the catalysts,[9] and the use of the catalysts,[10] have been reported Recently, two reviews about the development and application of chiral oxazaborolidines have appeared [11]

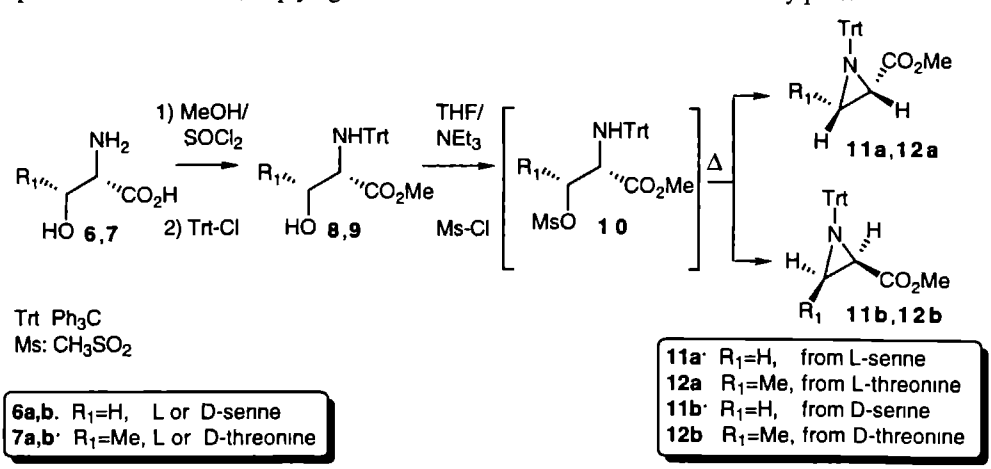
Cyclic amino alcohols, namely azetidine,[12] pyrrolidine,[13] and piperidine[14] derived carbinols **3**, **4** and **5**, respectively, have been studied extensively, as basis for 1,3,2-oxazaborolidine catalysts Our interest in chiral small-ring heterocycles, especially functionalized epoxides,[15] and aziridines,[16] was a reason to investigate the aziridine-2-alcohols **1** and **2** as precatalyst systems [17] Comparison of the asymmetric reductions with the oxazaborolidine catalysts derived from the

corresponding 6, 5, 4 and 3-membered cyclic aminoalcohols is clearly of interest. The reaction of choice for this comparison is reduction of prochiral ketones employing such oxazaborolidines.

4.2 Results and Discussion

Several approaches to the preparation of optically active aziridine-2-carboxylic esters, the precursors of the aziridine-2-tertiary alcohols **1** and **2**, are known.[18]. In 1972 Nakajima and coworkers[19] reported the synthesis of N-substituted aziridine-2-carboxylic acid esters, based on the Wenker[20] aziridine synthesis. In this modified Wenker procedure the hydroxy amino acids serine and threonine are used as the starting material. The hydroxy group in N-tritylated α-amino-acid esters **8** and **9** was first converted into the corresponding tosylate in pyridine as the solvent, and subsequent base treatment gave an intramolecular cyclization to yield the N-trityl-aziridine-2-carboxylic acid esters **11** and **12**, respectively, in a two-step procedure in moderate yields.[21] In a later study[22] Nakajima et al replaced tosyl chloride by mesyl chloride.

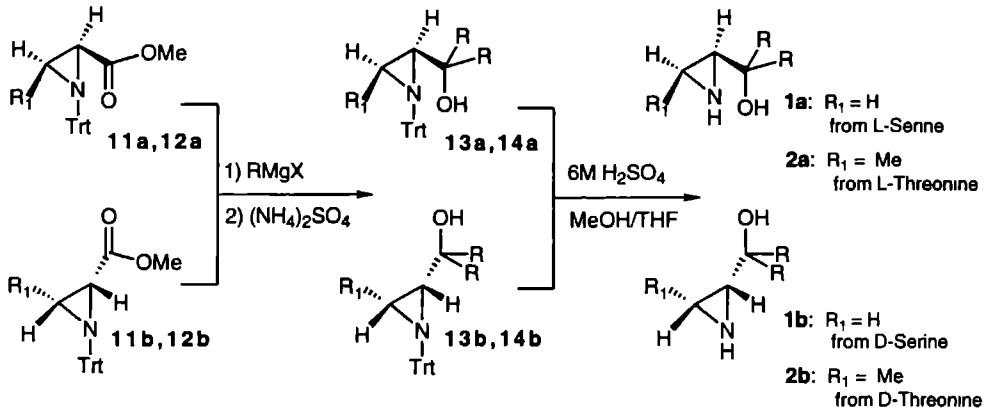
An improved synthesis of aziridine-2-carboxylic esters starting from naturally occurring enantiopure hydroxy amino acids based on a procedure described by Nakajima et al was developed. The convenient multigram 'one-pot procedure' of the synthesis of the N-trityl-aziridine-2-carboxylic esters (**11,12**) from N-trityl-serine and threonine methyl ester (**8,9**) makes use of mesyl chloride in THF, as depicted in scheme 4 1 The reaction is performed in THF at reflux temperature[23] for 48 h. with 2.1 equivalents of NEt_3 and 1 01 equivalent of mesyl chloride The crude product was isolated in a quantitative yield with a purity of 95% according to GLC and ^{1}H-NMR, and was used as such in further reactions. The optical rotation of **11a**, $[\alpha]^{20}_D$= -96 8° (c=1.1, MeOH), was in good agreement with the reported value[24] $[\alpha]^{20}_D$= -95.4° (c=1.1, MeOH) for this aziridine derivative. After recrystallisation the optical rotation, $[\alpha]^{20}_D$= +97 6° (c=1 1, MeOH), of aziridine **11b** derived from D-serine has the same value but with opposite sign as reported in the literature, implying that the obtained material is enantiomerically pure.



Scheme 4.1

The highly reproducible mesyl chloride method could also be applied successfully for the preparation of methyl (2S,3S)-1-trityl-3-methyl-2-aziridinecarboxylate (**12a**, R_1 = Me) from L-threonine and (2R,3R)-1-trityl-3-methyl-2-aziridinecarboxylate (**12b**, R_1 = Me) from D-threonine. The optical rotation of **12b**, $[\alpha]^{20}_D$: +97 4° (c=1, $CHCl_3$) has the same value as reported [25] $[\alpha]^{20}_D$: +98.0° (c=1, $CHCl_3$). The optical rotation of **12a**, $[\alpha]^{20}_D$= -97 1° (c=1, $CHCl_3$) has the

same value but opposite sign as reported for the aziridine derived from D-threonine. Thus, reaction of N-trityl-L and D-threonine methyl esters (**9a-b**, R_1 = Me) with mesyl chloride and NEt_3 in THF gave enantiopure aziridines (**12a,b**, R_1 = Me) in almost quantitative yields.



Scheme 4.2

The N-trityl-aziridine-2-carboxylic esters **11** and **12** were converted into the corresponding N-trityl-aziridine-2-carbinols **13** and **14** using phenylmagnesium bromide. Detritylation using sulfuric acid in methanol/THF gave enantiopure aziridine-2-tertiairy alcohols **1-2** in good yields[26] (see Table 4.1).

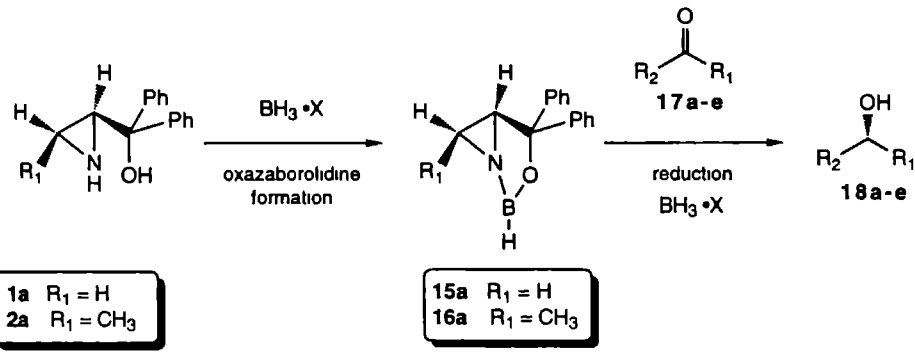
Table 4.1. Yields, Optical Rotation Values, and E.e.'s of the Aziridine Carbinols **13-14** and **1-2**.

Derivative of aminoacid:	Compound	R_1	R	$[\alpha]_D^{20}$ (c=1; $CHCl_3$)	Yield (%)	e.e. (%)
L-Serine	**13a**	H	Ph	-78.8°	(92)[a] 62[b]	>99[c]
L-Threonine	**14a**	Me	Ph	+22.5°	76[b]	>99[c]
D-Serine	**13b**	H	Ph	+82.8°	(86)[a] 68[b]	>99[c]
D-Threonine	**14b**	Me	Ph	-22.2°	72[b]	>99[c]
L-Serine	**1a**	H	Ph	-16.7°	(83)[a] 60[b]	>99[d,e]
L-Threonine	**2a**	Me	Ph	+82.2°	(90)[a] 72[b]	>99[d,e]
D-Serine	**1b**	H	Ph	+17.0°	(81)[a] 61[b]	>99[d,e]
D-Threonine	**2b**	Me	Ph	-82.8°	(95)[a] 83[b]	>99[d,e]

a) Crude yield. b) After purification by flash-column chromatography and recrystallisation. c) E.e.-determination using HPLC (Chiralcel OD; hexane/2-propanol=90:10). d) E.e.-determination using HPLC (Chiralcel OD; hexane/2-propanol=99:1). e) E.e.-determination using camphanoylchloride derivative with 400-MHz ^{1}H NMR.

The e.e.'s of the protected aziridine-2-tertiary alcohols **13** and **14** were determined by HPLC analysis using a chiral column (Chiralcel OD) and were higher than 99% in all cases. After the acidic removal of the trityl protecting group the aziridine-2-tertiairy alcohols **1** and **2** were isolated and then recrystallised to give enantiomerically pure **1** and **2** in 60-80% (Table 4.1). The enantiomeric purity of the deprotected aziridine-2-tertiary alcohols was determined by 400-MHz ^{1}H-NMR using camphanoyl chloride as a chiral derivatising agent and directly by HPLC (Chiralcel OD, hexane/2-propanol).

The azirıdine carbınols **1** and **2** were used for the reduction of prochıral ketones For this purpose they were converted ınto the corresponding oxazaborolıdınes by treatment wıth borane The thus *ın sıtu* formed boron heterocycles are the actual catalysts, which upon complexatıon wıth borane serve as the chıral reducıng agent (Scheme 4 3).



Scheme 4 3

In a recent paper of Stone et al [27] the effect of temperature, solvent and catalyst concentratıon ın the asymmetrıc catalytıc reductıon of prochıral ketones usıng the oxazaborolıdıne derıved from α,α-dıphenyl-2-pyrrolıdınemethanol (**4**) were evaluated It was found that maxımum e e 's were obtaıned at temperatures between 30 and 50°C and at lower temperatures (<30°C) the e e decreased consıderably, as was also observed ın the experıments descrıbed here

Table 4.2. Asymmetrıc Reductıon of Acetophenone **17a** wıth Oxazaborolıdınes **15a** Derıved from **1a** under Varıous Condıtıons

	Oxazaborolidine formation					Reduction			
Entry	T(°C)	X	BH_3-X (eq)	time (h)	Solvent	T(°C)	X	yield[a]	e.e.(%)[b,c]
1	20	THF	6	0 15	toluene	35	DMS	95	53 (R)
2	20	THF	6	0 15	THF	35	THF	90	76 (R)
3	55	THF	6	15	THF	35	THF	92	10 (R)
4	66	THF	6	2	THF	35	DMS	88	37 (R)
5	20	DMS	6	0 15	THF	35	DMS	90	72 (R)
6	55	DMS	6	15	THF	35	THF	93	87 (R)
7	55	DMS	3	15	THF	35	DMS	95	90 (R)
8	55	DMS	3	15	THF	0	DMS	88	81 (R)
9	66	DMS	1	15	THF	35	DMS	92	8 0 (R)
10	66	DMS	3	3	THF	35	DMS	90	37 (R)
11	66	DMS	3	15	THF	35	DMS	94	92 (R)
12	66	DMS	6	15	THF	35	DMS	92	95 (R)
13	66	DMS	6	90	THF	35	DMS	93	28 (R)
14	66	DMS	6	15	toluene	35	DMS	94	47 (R)

a) Isolated yıelds b) Determıned by GLC (PAS-1701) usıng the camphanoyl derıvatıve of 1-phenylethanol (**18a**) c) [**1a**] = 10 mol(%) d) DMS dımethylsulfıde

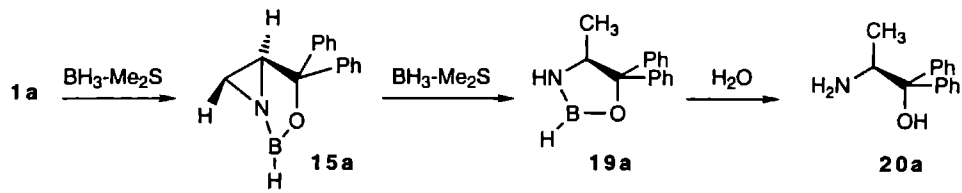
The azirıdine carbınols **1a,b** were converted *ın sıtu* ınto oxazaborolıdıne **15a,b** by reactıon wıth BH_3-Me_2S ın THF After heatıng at reflux for 15 h the solvent and excess borane sulfıde complex were removed The thus obtaıned catalyst was then dıssolved ın THF followed by BH_3-

Me_2S and the ketone substrate. The reduction to the secondary alcohols **18** takes place exothermally in a very short reaction time.

Reduction of acetophenone (**17a**, R_1=Ph, R_2=CH_3) by the oxazaborolidine derived from chiral aziridine carbinol **1a** (Scheme 4 3), was carried out under various reaction conditions (Table 4.2). Table 4 2 shows that the stereoselectivity of the reduction depends both on the temperature at which the reduction step is performed and on the conditions under which the chiral oxazaborolidine catalyst is prepared. Lowering the temperature of the reduction step results in a decrease in asymmetric induction (entry 7-8).

The enantioselectivity of the reduction is dependent on the formation time, temperature, and on the borane complex used (BH_3-THF, BH_3-S(Me)$_2$) during the *in situ* preparation of the catalyst. When the chiral oxazaborolidine was prepared *in situ* using BH_3-THF, the reduction resulted in (R)-1-phenylethanol (**18a**), with moderate enantiomeric purities in all cases.

When the oxazaborolidine **15a** was prepared using BH_3-DMS, product **18a** was obtained in high enantiomeric purities (e.e >90%) (entries 11,12). For the preparation of the chiral oxazaborolidine a reaction time of 15 h at reflux temperature (66°C) was found to give optimum results When shorter preparation times were used the e.e.'s were lowered (entry 10). Similarly, longer reaction times resulted in lower e.e's (entry 13). The fact that a lower asymmetric induction is obtained, when the aziridine carbinol is refluxed for 3 h with BH_3-DMS is possibly due to only a partial formation of the oxazaborolidine catalyst In the other case when the aziridine carbinol is heated at reflux for a longer period of time (90 h), the lowering in e.e is due to thermal disproportionation of the chiral oxazaborolidine (entry 13).



Scheme 4.4

During prolonged heating of the oxazaborolidine derived from precatalyst **1a**, reductive cleavage of the β-C-N bond of the aziridine ring took place, presumably yielding oxazaborolidine **19a** derived from (S)-2-amino-1,1-diphenylpropanol (Scheme 4 4). Hydrolysis of the reaction mixture yielded amino alcohol **20a** as was secured by ^{1}H-NMR and a mass-spectrum The optical rotation of **20a**, $[\alpha]^{20}_D$· -84 7° (c=1, $CHCl_3$), was in good agreement with the reported value[28] $[\alpha]^{20}_D$: -82.4° (c=1, $CHCl_3$) for this (S)-alanine derivative. The formation of **19a** explains the lower e.e during the reaction of acetophenone. The above observations indicate that during the formation of the oxazaborolidine catalyst **15a** using 6 equivalents of BH_3-THF in THF at reflux temperature for 15 h a mixture of **15a** and **19a** is produced. According to GLC the ratio of **15a** and **19a** amount to 60:40 Probably catalyst **15a** is the most effective one and responsible for the fast asymmetric reductions with high e e's. Prolonged heating (*e.g.* 90 h) results in almost complete reductive cleavage to **19a**. This boron heterocycle also catalyses the asymmetric reductions but is much less effective (e.e = 28%, entry 13).

The reduction of acetophenone (**17a**) by the oxazaborolidine derived from chiral azirıdine carbinol **2a** (Scheme 4.3), was carried out under various reaction conditions as well (Table 4 3). The data in Table 4 3 indicate that for the catalyst derived from **2a** the stereoselectivity of the reduction reaction is also dependent on the temperature at which the reduction step is performed and on the conditions used during oxazaborolidine catalyst preparation At low temperature (0°C)

(entry 5) as well as high temperatures (entries 10-11), the reduction results in a moderate asymmetric induction similarly as was observed for the catalyst derived from **1a**

The stereoselectivity of the reduction was also dependent on the formation time, solvent, temperature, and on the type of borane complex used (BH_3-THF, BH_3-$S(Me)_2$) during the *in situ* preparation of the catalyst When the chiral oxazaborolidine was prepared *in situ* from BH_3-THF in THF as the solvent, the reduction gave (R)-1-phenylethanol (**18a**) with moderate enantiomeric purities in all cases (entries 1-3) On the other hand, when the preparation of the oxazaborolidine was performed with BH_3-THF in toluene in 10 min , product **18a** was obtained in high enantiomeric purities (e e > 90%) (entries 8-9) A reaction time of 10 min at room temperature in toluene for the preparation of the chiral oxazaborolidine **16a** gave optimal results When longer preparation times were used the e e 's were lowered (entry 12) as well as was the case when higher temperatures were applied (entries 10,11,13)

Table 4.3. Asymmetric Reduction of Acetophenone **17a** with Oxazaborolidines Derived from **2a** under Various Conditions

	Oxazaborolidine formation					Reduction			
Entry	**T(°C)**	**X**	**BH_3-X (eq)**	**time (h)**	**Solvent**	**T(°C)**	**X**	**yield[a]**	**e.e.(%)[b]**
1	0	THF	15	0 5	THF	0	THF	92	6 0 (R)[c]
2	30	THF	15	0 5	THF	35	THF	91	52 (R)[c]
3	66	THF	15	0 5	THF	66	THF	88	60 (R)[c]
4	30	THF	3	0 5	toluene	35	THF	93	79 (R)[c]
5	30	THF	3	0 5	toluene	0	THF	90	64 (R)[c]
6	20	DMS	3	0 5	toluene	35	DMS	90	69 (R)[c]
7	20	THF	1 1	0 15	toluene	35	DMS	95	66 (R)[d]
8	20	THF	2	0 15	toluene	35	DMS	88	94 (R)[d]
9	20	THF	3 2	0 15	toluene	35	DMS	92	90 (R)[d]
10	66	THF	3	0 15	toluene	66	DMS	90	46 (R)[d]
11	110	THF	3	0 15	toluene	110	DMS	94	49 (R)[d]
12	20	THF	3	15	toluene	35	DMS	91	34 (R)[c]
13	50	THF	3	15	toluene	35	DMS	95	42 (R)[c]

a) Isolated yields b) Determined by GLC (PAS 17 01) using the camphanoyl derivative of 1 phenylethanol (**18a**)
c) [catalyst **16a**] = 10 mol (%) d) [catalyst **16a**] = 5 mol (%) e) DMS = dimethylsulfide

The decrease in asymmetric induction, when the aziridine carbinol is reacted with BH_3-THF for longer times and higher temperatures is possibly due to disproportionation of the chiral aziridine carbinol borane complex However, in this case no disproportionation product could be isolated

The results from Table 4 2 and 4 3 show that the formation of the oxazaborolidines derived from **1** and **2** need entirely different reaction conditions to achieve optimal results in the enantioselective reduction of prochiral ketones For the oxazaborolidines from **2a, b**, optimum results were obtained when the precatalysts **2a** and **2b** and 2 equivalents of BH_3-THF were mixed in toluene at room temperature for 10 min, immediately followed by the reducing agent BH_3-SMe_2 in toluene The optimum reaction conditions described for **1a, b** gave only moderate e e 's (30%) when applied for **2a, b** When the optimum reaction conditions for the preparation of oxazaborolidines **16a, b** were used for **15a, b** the enantiomeric purity of alcohol **18a** was rather low (53%) These findings indicate that the *cis* methyl-group in the precatalysts **2a, b**, which is absent in the precatalysts **1a, b**, has an enormous effect on the asymmetric induction capability of

the chiral catalyst in the reduction of prochiral ketones. The difference in reactivity between **1a, b** and **2a, b** is highly remarkable and deserves further elaboration.

The asymmetric reduction of several prochiral ketones (**17a-e**) to the corresponding chiral secondary alcohols (**18a-e**) by the chiral oxazaborolidines derived from **1-2** was then investigated (Scheme 4.3). The reduction reactions were carried out using the optimum reactions conditions for the oxazaborolidines derived from **1** (Table 4.2) and **2** (Table 4.3) in the enantioselective reduction of acetophenone (**17a**).

The aziridine-2-carbinols **1a, b** (L-and D-serine derived precatalysts) were converted into the corresponding oxazaborolidines **15a, b** by an '*in situ*' reaction (Table 4.2, entry 12) with an excess of borane-Me_2S complex in THF at reflux temperature for 15 h, followed by removal of the solvent and excess borane *in vacuo* (method I). In the case of precatalysts **2a, b** (derived from L- and D-threonine) the oxazaborolidines **16a, b** were prepared in toluene at room temperature (method II) with 2 equiv of BH_3-THF in toluene in 10 min. (Table 4.3, entry 8).

The procedure for the reduction of the prochiral ketones **17a-e** involves a fast addition of the ketone to a THF (serine derived catalysts) or toluene (threonine derived catalysts) solution of the catalyst-BH_3-Me_2S complex at room temperature. This operation caused a direct raise of the temperature of the reaction mixture to ca 35°C and remained constant during the reduction reaction. The progress of the reaction was monitored by TLC. In most cases the ketones **17a-e** were converted into the corresponding chiral alcohols **18a-e** within 5 min. in high chemical yields.

Table 4.4. Results of the Reduction of Ketones **17a-e** with Oxazaborolidines Derived from **1-2** and **4** under Optimum Conditions.

Entry	No	Ketone	catalyst	Solvent	yield[a]	e.e.(%)	Config
			1a	THF	92	94[b,d]	R
1	**17a**	acetophenone	**1b**	THF	90	92[b,d]	S
			2a	toluene	92	94[b,d]	R
			2b	toluene	93	93[b,d]	S
			4	THF	92	92[b,d]	R
			4	toluene	90	90[b,d]	R
2	**17b**	*p*-methyl	**1a**	THF	93	92[c]	R
		acetophenone	**2b**	toluene	92	91[c]	S
3	**17c**	*p*-methoxy	**1a**	THF	89	86[d]	R
		acetophenone	**2b**	toluene	88	87[d]	S
4	**17d**	benzylacetone	**1b**	THF	90	57[d]	S
			2a	toluene	92	63[d]	R
5	**17e**	α-tetralone	**1b**	THF	88	79[c,d]	S
			2b	toluene	90	64[d]	S

a) Isolated yields. b) Determined by GLC (PAS-1701) using the camphanoyl derivative of 1-phenylethanol (**18a**). c) Determined by the optical rotation, alcohol from **17b** (ref. 29) and alcohol from **17e** (ref. 30). d) Determined by HPLC-analysis (See experimental).

The enantiomeric purity of alcohol **18a** was determined by GLC using the camphanoyl derivative of **18a**, and by HPLC using a chiral column (Daicel Chiralcel OD). Both methods gave identical results. The absolute configuration of the alcohol was deduced from measurement of its optical rotation. The enantiomeric purity of alcohols **18b** was determined by comparison of the value of the optical rotations with those reported in the literature. The e.e.'s of chiral alcohols **18c-e** were determined by HPLC (Chiralcel OD). Commercially available (S)-2-α,α-diphenyl-2-

pyrrolidinemethanol (**4**) was used for comparison under the same conditions as described above. The results of the ketone reductions are collected in Table 4.4.

The results of these reductions, summarized in Table 4.4, show that ketones **17a**, **17b**, **17c**, having an aromatic ring attached to the carbonyl group, were reduced in good chemical and optical yields. Ketone **17e**, a bicyclic aromatic ketone, gave a moderate asymmetric induction (65%, method I).

In order to explain the high enantioselectivities in the reductions using oxazaborolidines derived from **1**, the model depicted in Figure 4.1 is proposed. In this model the boron atom of the BH_3 is coordinated to the nitrogen atom and the oxygen atom of the prochiral ketone is coordinated to the boron atom of the oxazaborolidine. This model resembles that proposed[5-6] for the oxazaborolidine derived from (S)-2-α,α-diphenyl-2-pyrrolidinemethanol (**4**). (see also chapter 2 for relevant literature).

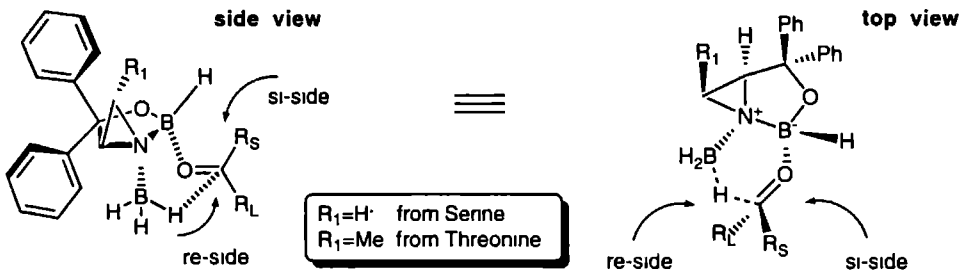


Figure 4.1

The hydride transfer is suggested to take place *via* a six-membered ring transition state, which has a twisted boat conformation as was established by *ab initio* calculations[31] on the oxazaborolidine derived from **4** by Nevalainen.

For a further development of these catalysts derived from aziridine carbinols **1** and **2** it would be appropriate to use a non-reductive preparation for the oxazaborolidines derived from **1** and **2** employing methylboronic acid,[32] trimethylboroxine[33] and other alkylboronates [34] An advantage of using alkylboronates in the preparation of oxazaborolidines is that the catalysts are expected to be stable in air, in analogy with the oxazaborolidines derived from (S)-2-α,α-diphenyl-2-pyrrolidinemethanol (**4**), and can be isolated in pure form.

4.3 Conclusion

The synthesis of a new class of chiral precatalysts, *viz.* aziridine-2-carbinols **1** and **2**, which can conveniently be converted into the corresponding oxazaborolidines is described. These new catalysts are attractive because they are readily available in both enantiomeric forms, starting from L-and D-serine and L-and D-threonine, respectively.

The enantioselective reduction of prochiral ketones **17a-c** with precatalysts **1**, **2**, and **4** using the optimum reaction conditions took place with high e.e's (>90%) The results with the three-membered ring derived catalysts gave similar e.e.'s as the five membered L-proline (**4**) derived catalyst.

4.4 Experimental

General methods Optical rotations were determined with a Perkin-Elmer automatic polarimeter, model 241 MC using 1% solutions at 20°C in the solvents indicated Melting points were determined using a Reichert thermopan microscope equipped with crossed polarisers, and are uncorrected Thin-layer chromatography (TLC) on pre-coated plates of silica gel (Merck) was performed in the solvent mixtures as indicated Detection was performed with UV (254 nm) and by spraying with an ammonium molybdene and concentrated H_2SO_4 solution in water and

subsequent heating at 140°C Column chromatography was performed on Silicagel 60H (Merck) with the eluents indicated A pressure of 1 5-2 0 bar was used to obtain the necessary flowrate GLC was conducted with a Hewlett-Packard HP5890A and HP 5790A gas chromatograph, using a capillary column (25m) of HP-1 and PAS-1701, a temperature program from 100-250°C at 15°C/min, followed by 10 min at 250°C (isothermal), and nitrogen at 2 ml/min (0 5 atm) as the carrier gas. The instruments were connected to a HP 3396 or HP 3390 calculating integrator, respectively ^{1}H and ^{13}C NMR were performed on a Bruker AC 100 (100 MHz, FT) and AM 400 (400 MHz, FT) spectrometer, respectively, with solutions in $CDCl_3$ (internal Me_4Si) IR spectra were determined on a Perkin-Elmer 298 spectrophotometer Elemental analyses were performed on a Carlo Erba Instruments CHNS-O EA 1108 element analyser Electron impact and Chemical ionisation mass spectra, induced with methane gas at 200°C and emission current 0 5 mA, were determined on a VG 7070E spectrometer E.e 's were determined by HPLC using a Chiralcel OD column with the eluents indicated (eluent n-hexane/2-propanol)

Chemicals Diethyl ether was pre-dried over calcium chloride, then distilled from calcium hydride Hexane and petroleum ether (60-80) were distilled from sodium hydride Dichloromethane was distilled from phosphorous pentoxide Tetrahedrofuran was distilled from lithium aluminum hydride Triethylamine was distilled from potassium hydroxide All other solvents were either P A or "reinst ' quality

Methyl (2S)-1-trityl-2-aziridinecarboxylate (11a, R_1=H)

Compound **8a** (R_1=H) (93 8 g, 259 mmol) was dissolved in THF (700 mL) at room temperature Triethylamine (83 0 mL, 574 mmol, 2 2 equiv) was added, followed by the gradual addition of mesyl chloride (20 0 mL, 262 mmol, 1 01 equiv) during a period of 15 min The mixture was left for 30 min at 20°C Then the temperature was raised to 66°C and the reaction mixture was heated at reflux for 48 h The reaction was monitored by capillary GLC After 48 h the reaction mixture was cooled to room temperature and concentrated Then 300 mL of ethyl acetate was added, followed by extraction with an aqueous citric acid solution (10%) (3x 100 mL) and a saturated sodium bicarbonate solution (3x 50 mL) The combined organic layers were dried ($MgSO_4$) and concentrated Yield 100% (92 0 g, 259 mmol) Purity 93% according to capillary GLC, TLC R_f = 0 7 (CH_2Cl_2) For characterization 1 g of the crude material was recrystallised from MeOH/NEt_3 (50 mL/15 drops) yielding material with a purity of 99 5% according to GLC The NEt_3 was needed to prevent detritylation of the product during the purification procedure $[\alpha]^{20}_D$ -86 2° (c=1, $CHCl_3$), $[\alpha]^{20}_D$, -96 8° (c=1 1, MeOH) m p 127-129°C Calc for $C_{23}H_{21}O_2N$ (343 43) C 80 44, H 6 16, N 4 08 %, found C 80 11, H 6 23, N 4 07 % MS (EI) m/e 343 (M^+, 0 04%), 266 (M^+-Ph, 2 9%), 243 (Trt^+, 100%), 165 (Trt-Ph^+, 80%), 77 (Ph^+, 15%) ^{1}H NMR (100 MHz in $CDCl_3$), δ 7 55-7 21 (m, 15H, aromatic H, Trt), 3 76 (s, 3H, OCH_3), 2 24 (dd, 1H, J = 1 6 and 2 7Hz, βCH, Azy), 1 89 (dd, 1H, J = 6 2 and 2 7Hz, αCH, Azy), 1 40 (dd, 1H, J = 1 6Hz and 6 2Hz, βCH, Azy) ppm ^{13}C NMR (25 2 MHz in $CDCl_3$), δ 171 9 (C=O ester), 143 6-127 0 (aromatic C), 74 4 (Ph_3C-N), 52 1 (OCH_3 ester), 31 7 (αCH, Azy), 26 7 (βCH_2, Azy) ppm IR (KBr) υ 3100-3000, 1600 (aromatic), 3000 - 2900 (alkyl), 1740 (C=O) cm^{-1}

Methyl (2R)-1-trityl-2-aziridinecarboxylate (11b, R_1=H)

Using the same procedure as described for **11a**, compound **8b** (R_1=H) (43 1 g, 119 mmol) was converted into **11b** in a quantitative manner (40 5 g, 118 mmol) with a purity of 95% according to capillary GLC For characterization, 1 g of the crude material was recrystallised from MeOH/NEt_3 (50 mL/15 drops) yielding the material with a purity of 99 5% according to GLC $[\alpha]^{20}_D$= +88 5° (c=1, $CHCl_3$), $[\alpha]^{20}_D$= +97 6° (c=1 1, MeOH) m p 125-127°C Calc for $C_{23}H_{21}O_2N$ (343 43) C 80 44, H 6 16, N 4 08 %, found C 80 46, H 6 18, N 4 11 % MS (EI) m/e 343 (M^+, 0 05%), 266 (M^+-Ph, 2 6%), 243 (Trt^+, 100%), 165 (Trt-Ph^+, 82%), 77 (Ph^+, 14%) ^{1}H NMR (100 MHz in $CDCl_3$), δ 7 55-7 10 (m, 15H, aromatic H, Trt), 3 74 (s, 3H, OCH_3), 2 25 (dd, 1H, J =1 6 and 2 7Hz, βCH, Azy), 1 89 (dd, 1H, J = 6 2 and 2 7Hz, αCH, Azy), 1 40 (dd, 1H, J = 1 6 and 6 2Hz, βCH, Azy) ppm ^{13}C NMR (25 2 MHz in $CDCl_3$), δ 172 1 (C=O ester,), 143 8-127 1 (aromatic C), 74 6 (Ph_3C-N), 52 2 (OCH_3 ester), 31 9 (αCH, Azy), 26 8 (βCH_2, Azy) ppm IR (KBr) υ 3100-3000, 1600 (aromatic), 3000 - 2900 (alkyl), 1740 (C=O) cm^{-1}

Methyl (2S, 3S)-1-trityl-3-methyl-2-aziridinecarboxylate (12a, R_1=Me)

Using the same procedure as described for **11a**, compound **9a** (R_1=Me) (23 4 g, 62 4 mmol) was converted into **12a** in a quantitative manner (22 3 g, 62 4 mmol) with a purity >90% according to NMR The reaction was monitored using TLC, because the aziridine was not stable using capillary GLC For characterization, 1 g of the crude material was recrystallised from MeOH/hexane yielding a clear crystalline compound $[\alpha]^{20}_D$= -97 1° (c=1, $CHCl_3$) m p 112-113°C Calc for $C_{24}H_{23}O_2N$ (357 43) C 80 64, H 6 48, N 3 92 %, found C 80 56, H 6 42, N 3 96 % MS (EI) m/e 298 (M^+-CO_2Me, 0 3%), 280 (M^+-Ph, 0 6%), 243 (Trt^+, 100%), 165 (Trt-Ph^+, 50%), 77 (Ph^+, 5%) ^{1}H NMR (100 MHz in $CDCl_3$), δ 7 58-7 10 (m, 15H, aromatic H, Trt), 3 74 (s, 3H, OCH_3), 1 88 (d, 1H, J = 6 3Hz αCH, MeAzy), 1,69-1 56 (m, 1H, βCH, MeAzy), 1,36 (d, 3H, J = 5 2Hz, CH_3) ppm ^{13}C NMR (25 2 MHz in $CDCl_3$), δ 170 7 (C=O ester,), 143 9-126 7 (aromatic C), 75 1 (ϕ_3C-N), 51 8 (OCH_3 ester), 36 0 (αCH,

MeAzy), 34 6 (βCH, MeAzy), 13 4 (CH_3, Azy) ppm IR (KBr) υ 3100-3000, 1600 (arom), 3000-2900 (alkyl), 1740 (C=O) cm^{-1}

Methyl (2R, 3R)-1-trityl-3-methyl-2-aziridinecarboxylate (12b, R_1=Me)
Using the same procedure as described for **11a**, compound **9b** (R_1=Me) (73 4 g, 195 mmol) was converted into **12b** in a quantitative manner (69 6 g, 195 mmol) with a purity >90% according to NMR
The reaction was monitored using TLC, because the aziridine was not stable using capillary GLC For characterization, 1 g of the crude material was recrystallised from MeOH/hexane yielding a clear crystalline compound $[\alpha]^{20}_D$= +97 4° (c=1, $CHCl_3$) m p 112-113 5°C Calc for $C_{24}H_{23}O_2N$ (357 43) C 80 64, H 6 48, N 3 92 %, found C 80 81, H 6 28, N 3 92 % MS (EI) m/e 298 (M^+-CO_2Me, 0 7%), 280 (M^+-Ph, 1 6%) 243 (Trt^+, 100%), 165 (Trt-Ph^+, 84%), 77 (Ph^+, 17%) ^{1}H NMR (100 MHz in $CDCl_3$), δ 7 58-7 10 (m, 15H, aromatic H, Trt), 3 74 (s, 3H, O$\underline{C}H_3$), 1 88 (d, 1H, J = 6 3Hz αCH, MeAzy), 1,69-1 56 (m, 1H, βCH, MeAzy), 1,36 (d, 3H, J = 5 2Hz, CH_3) ppm ^{13}C NMR (25 2 MHz in $CDCl_3$), δ 170 6 (C=O ester), 143 7-126 6 (aromatic C), 74 9 (Ph_3C-N), 51 7 (O$\underline{C}H_3$ ester), 35 7 (αCH, MeAzy), 34 7 (βCH, MeAzy), 13 3 (CH_3, Azy) ppm IR (KBr) υ 3100-3000, 1600 (arom), 3000 - 2900 (alkyl), 1740 (C=O) cm^{-1}

For the Grignard reactions all glassware was dried at 140°C overnight, and flame dried under vacuum using a Schlenk apparatus All reactions were carried out under a static pressure of argon

1-Trityl-(-)-(2S)-aziridine-2yl-diphenylmethanol (13a)
To a stirred suspension of magnesium turnings (2 52 g,104 mmol, 3 4 equiv) in ether (20 ml) was gradually added bromobenzene (10 8 ml, 103 mmol, 3 4 equiv) in 15 mL ether The magnesium was activated by magnetically stirring overnight under an argon atmosphere[35] After heating the Grignard reagent for 1 5 hours compound **11a** (R_1=H) (10 3 g, 29 9 mmol) in THF (20 mL) was added dropwise over a period of 20 min The reaction was monitored with capillary GLC and TLC (CH_2Cl_2) After 1 5 h the reaction was quenched with a saturated $(NH_4)_2SO_4$ solution (30 mL) followed by the evaporation of the organic solvents THF and ether The residue was extracted with ether (3x 150 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated Yield 92% (12 9 g, 27 5 mmol) of a yellow crystalline compound The crude product was purified by flash column chromatography (hexane/ethylacetate 12 1) and NEt_3 (1 mL/L) was added to the eluens to prevent detritylation of the product during the purification procedure Recrystallisation from MeOH/NEt_3 (50mL/15 drops) afforded 8 7 g (62%) of **13a** m p 133 5-134 5°C $[\alpha]^{20}_D$ = -78,8° (c=1, $CHCl_3$) Calc for $C_{34}H_{29}NO$ (467 61) C 87 33, H 6 25, N 3 00 %, found C 86 22, H 6 26, N 2 96 % MS (EI) m/e 390 (M-$C_6H_5^+$ 0 5%), 243 (Trt^+, 100%), 165 (Trt-Ph^+, 53 5%), 183 (($(C_6H_5)_2$C-OH^+, 30 4%), 105 ($C_6H_5CO^+$, 32 0%), 91 ($C_7H_7^+$, 8 0%), 77 ($C_6H_5^+$, 25 6%) ^{1}H NMR (100 MHz in $CDCl_3$), δ 7 40-7 02 (m, 25H, aromatic H, Trt, Phenyl), 4 36 (s, 1H, OH), 2 29 (dd, 1H, J = 6 3 and 3 2Hz, αCH, Azy), 2 00 (d, 1H, J = 3 2Hz, bCH, Azy), 1 25 (d,1H, J = 6 3Hz, βCH, Azy) ppm ^{13}C NMR (25 2 MHz in $CDCl_3$), δ 147 0-125 9 (aromatic C), 74 0 and 73 9 (Ph_3CN and COH alcohol), 41 5 (αCH, Azy), 23 6 (βCH, Azy) ppm IR (KBr) υ 3500-3300 (OH), 3100-3000, 1600 (aromatic) cm^{-1}

1-Trityl-(+)-(2R)-aziridine-2yl-diphenylmethanol (13b)
Using the same procedure as described for **13a**, compound **11b** (R_1 =H) (10 0 g, 29 2 mmol) was converted into **13b** using a Grignard reaction The Grignard reagent was prepared by using magnesium turnings (2 51 g, 103 mmol) and bromobenzene (10 7mL, 102 mmol) in ether (20 mL) Yield 86% (11 7 g, 25 1 mmol) of a yellow crystalline compound The crude product was purified by flash column chromatography (petroleum ether/ethylacetate 12 1) and NEt_3 (1 mL/L) was added to the eluens to prevent detritylation of the product during the purification procedure Recrystallisation from MeOH/NEt_3 (50mL/15 drops) afforded 9 5 g (68%) of **13b** m p 129-133 °C $[\alpha]^{20}_D$ = +82 8° (c=1, $CHCl_3$) Calc for $C_{34}H_{29}NO$ (467 61) C 87 33, H 6 25, N 3 00 %, found C 86 58, H 6 25, N 3 04 % MS (EI) m/e 390 (M^+-C_6H_5, 2 1%), 243 (Trt^+, 100%), 183 (($(C_6H_5)_2$C-OH^+, 48 0%), 165 (Trt-Ph^+, 61 0%), 105 ($C_6H_5CO^+$, 32 5%), 91 ($C_7H_7^+$, 11 7%), 77 ($C_6H_5^+$, 24 0%) ^{1}H NMR (100 MHz in $CDCl_3$), δ 7 46 - 7 11 (m, 25H, aromatic H, Trt, Phenyl), 4 44 (s, 1H, OH), 2 35 (dd, 1H, J = 6 3 and 3 2Hz, αCH, Azy), 2 08 (d, 1H, J = 3 2Hz, βCH, Azy), 1 33 (d, 1H, J = 6 3Hz, βCH, Azy) ppm ^{13}C NMR (25 2 MHz in $CDCl_3$), δ 146 9-125 7 (aromatic C), 74 0 and 73 9 (Ph_3CN and COH alcohol), 41 4 (αCH, Azy), 23 8 (βCH, Azy) ppm IR (KBr) υ = 3500-3300 (OH), 3100-3000, 1600 (aromatic) cm^{-1}

(-)-(2S)-aziridine-2yl-diphenylmethanol (1a)
Compound **13a** (R_1=H) (2 58 g, 5 51 mmol) was dissolved in a mixture of THF and MeOH (1 1, 10 mL) at roomtemperature A H_2SO_4 solution (6M, 20 mL) was carefully added, and the reaction mixture was stirred overnight The reaction was monitored by TLC (PE/EtOAc = 1 1) After 20h the reaction mixture was concentrated, followed by the extraction with ether (3x 20 mL) An aqueous NaOH solution (20%, 5 mL) was added to the acidic

aqueous layer until basic and this aqueous layer was extracted with chloroform (3x 30 mL) The combined chloroform layers were dried ($MgSO_4$) and concentrated *in vacuo* Yield 75% (927 mg, 4 11 mmol) of a light yellow crystalline compound Purity 93% according to capillary GLC Recrystallisation from ethylacetate afforded 740 mg (60%) of **1a** m p 165 -167 °C $[\alpha]^{20}_D$ = -16 7° (c=1, $CHCl_3$) Calc for $C_{15}H_{15}NO$ (225 29) C 79 97, H 6 71, N 6 22 %, found C 79 39, H 6 61, N 6 17 % MS (EI) m/e 225 (M^+, 1 7%), 207 (M^+-H_2O, 32 0%), 183 (($C_6H_5)_2C$-OH^+, 65 8%), 165 (Trt-Ph^+, 12 7%), 148 (M^+-Ph, 7 6%), 105 ($C_6H_5CO^+$, 100%), 91 ($C_7H_7^+$, 9 5%), 77 ($C_6H_5^+$, 75 6%), 43 (M^+-183, 37 3%) ^{1}H NMR ($CDCl_3$), δ 7 51 - 7 11 (m, 10H, aromatic H, Phenyl), 2 80 (dd, 1H, J = 6 0 and 3 6Hz, αCH, Azy), 1 86 (d, 1H, J = 6 0Hz, βCH, Azy), 1 74 (d,1H, J = 3 6Hz, βCH, Azy) ppm ^{13}C NMR ($CDCl_3$), δ 147 2-127 0 (arom C), 74 3 (COH), 37 0 (αCH, Azy), 21 9 (βCH, Azy) ppm IR (KBr) υ = 3500-3300 (OH), 3100-3000, 1600 (aromatic) cm^{-1}

(+)-(2R)-aziridine-2yl-diphenylmethanol (1b)
Using the same procedure as described for **1a**, compound **13b** (R_1=H) (5 71 g, 12 20 mmol) was dissolved in a mixture of THF and MeOH (1 l, 20 mL) and converted into **1b** using an H_2SO_4 solution (6M, 30 mL) Yield 81% (2 24 g, 9 93 mmol) of a light yellow crystalline compound Purity 94% according to capillary GLC Recrystallisation from toluene afforded 1 37 g (61%) of **1b** m p 164 -167 °C $[\alpha]^{20}_D$ = +17 0° (c=1, $CHCl_3$) Calc for $C_{15}H_{15}NO$ (225 29) C 79 97, H 6 71, N 6 22 %, found C 79 99, H 6 63, N 6 22 % MS (EI) m/e 225 (M^+, 1 7%), 207 (M^+-H_2O, 28 7%), 183 (($C_6H_5)_2C$-OH^+, 58 8%), 165 (Trt-Ph^+, 15 9%), 148 (M^+-77, 6 9%), 105 ($C_6H_5CO^+$, 100%), 91 ($C_7H_7^+$, 9 4%), 77 ($C_6H_5^+$, 81 8%), 43 (M^+-183, 33 6%) ^{1}H NMR (100 MHz in $CDCl_3$), δ 7 51-7 25 (m, 10H, aromatic H, fenyl), 2 89 (dd, 1H, J = 6 0 and 3 6Hz, αCH, Azy), 1 84 (d, 1H, J = 6 0Hz, βCH, Azy), 1 73 (d,1H, J = 3 6Hz, βCH, Azy) ppm IR (KBr) υ = 3500 -3300 (OH), 3100-3000, 1600 (aromatic) cm^{-1}

(S)-2-amino-1,1-diphenylpropanol (20a)
To a solution of **1a** (56mg, 0 25mmol) in THF (10 mL) a BH_3-Me_2S solution in THF (750µL, 2M, 1 5 mmol) was added This solution was heated at reflux temperature for 90 h, followed by removal of the solvent and excess BH_3-Me_2S *in vacuo* THF (3 5 mL) was added to the white solid catalyst, followed by BH_3-Me_2S in THF (1 25 mL, 2M, 2 5 mmol) and the immediate addition of the ketone **17a** (2 5 mmol) After 5 min the ketone **17a** had been consumed (TLC) and the reaction was quenched with MeOH (1 25 mL) Dilute sulfuric acid (4 ml, 1M) was added, followed by the removal of the organic solvents *in vacuo* The aqueous residue was extracted with ether (3x) and the collected organic layers were washed with a saturated $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated to give the chiral alcohol **18a** in high chemical yields and with an entiomeric excess of 28% A 2M NaOH solution (5 mL) was added to the acidic water residue and extracted with chloroform (3x) The collected organic layers were washed with a saturated $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated to give the chiral amino alcohol **20a** as white crystalline compound Purity 95% according to capillary GLC m p 88-95 °C $[\alpha]^{20}_D$ 84 7 (c=1, $CHCl_3$) (literature value [36] $[\alpha]^{20}_D$ -82 4 (c=0 814, $CHCl_3$) MS (EI) m/e 183 (Ph_2C OH^+, 5 3%), 165 (Trt-Ph^+, 4%), 105 ($C_6H_5CO^+$, 18%), 77 ($C_6H_5^+$, 16 0%), 44 ($CH_3CHNH_2^+$, 100%) ^{1}H NMR (100 MHz in $CDCl_3$), δ 7 6-7 1 (m, 10H, aromatic H, fenyl), 4 06 (q, 1H, αCH, J = 6 3 Hz), 2 0 (bs, 1H, OH), 0 86 (d, 3H, J = 6 3 Hz, CH_3) ppm IR (KBr) υ 3500 -3400 (OH), 3100-3000, 1600 (aromatic) cm^{-1}

1-Trityl-(+)-3-methyl-(2S,3S)-aziridine-2yl-diphenylmethanol (14a)
To a stirred suspension of magnesium turnings (1 49 g, 61 2 mmol, 4 equiv) in THF (75 ml) was gradually added bromobenzene (6 5 ml, 61 2 mmol, 4 equiv) The magnesium was activated by magnetic stirring overnight under an argon atmosphere After heating the Grignard reagent for 30 min compound **12a** (R_1=Me) (5 47 g, 15 3 mmol) in THF (25 mL) was added dropwise over a period of 20 min The reaction was monitored with TLC (hexane/ethylacetate = 3 1) After 1 5 h the reaction was quenched with a saturated NH_4Cl solution (50 mL) The crude reaction mixture was extracted with ether (3x 100 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated The crude product was purified by flash column chromatography (hexane/ethylacetate 3 1) Recrystallisation from hexane/ether afforded 5 6 g (76%) of **14a** m p 174-175°C $[\alpha]^{20}_D$ = +22 7° (c=1, $CHCl_3$) Calc for $C_{35}H_{31}NO$ (481 637) C 87 28, H 6 49, N 2 91 %, found C 87 31, H 6 68, N 2 96 % MS (EI) m/e 481 (M^+, 0 1%), 243 (Trt^+, 100%), 183 (($Ph)_2C$-OH^+, 37 2%), 165 (Trt-Ph^+, 39 8%), 105 ($C_6H_5CO^+$, 23 5%), 91 ($C_7H_7^+$, 5%), 77 ($C_6H_5^+$, 14 1%) ^{1}H NMR (100 MHz in $CDCl_3$), δ 7 32-7 02 (m, 25H, aromatic H, Trt, Phenyl), 4 95 (s, 1H, OH), 2 22 (d, 1H, J = 6 3 Hz, αCH, Azy), 1 68 (m, 1H, βCH, Azy), 1 19 (d, 3H, J = 5 7Hz, CH_3) ppm ^{13}C NMR (25 2 MHz in $CDCl_3$), δ 148 6-125 7 (aromatic C), 75 3 and 73 6 (Ph_3CN and COH alcohol), 45 3 (αCH, MeAzy), 32 0 (βCH, MeAzy) 13 7 (CH_3, Azy) ppm IR (KBr) υ = 3500 -3300 (OH), 3100-3000, 1600 (aromatic), 3000-2900 (alkyl) cm^{-1}

1-Trityl-(-)-3-methyl-(2R,3R)-aziridine-2yl-diphenylmethanol (14b)
Using the same procedure as described for **14a**, compound **12b** (R_1 =Me) (10 0 g, 28 0 mmol) in THF (50 mL) was converted into **14b** using a Grignard reaction The Grignard reagent was prepared by using magnesium turnings (2 72 g, 112 mmol) and bromobenzene (11 8 mL, 112 mmol) in THF (150 mL) The crude product was purified by flash column chromatography (hexane/ethylacetate 3 1) Recrystallisation from ether/hexane afforded 9 7 g (72%) of **14b** m p 174 5-175 5°C $[\alpha]^{20}_D$ = -22 2° (c=1, $CHCl_3$) Calc for $C_{35}H_{31}NO$ (481 637) C 87 28, H 6 49, N 2 91 %, found C 87 18, H 6 73, N 2 96 % MS (EI) m/e 481 (M^+, 0 01%), 243 (Trt^+, 100%), 183 ($(Ph)_2C\text{-}OH^+$, 43 9%), 165 (Trt-Ph^+, 40%), 105 ($C_6H_5CO^+$, 24 3%), 91 ($C_7H_7^+$, 5%), 77 ($C_6H_5^+$, 13 8%) ^1H NMR (100 MHz in $CDCl_3$), δ 7 34-7 03 (m, 25H, aromatic H, Trt, Phenyl), 4 85 (s, 1H, OH), 2 22 (d, 1H, J = 6 3 Hz, αCH, Azy), 1 67 (m, 1H, βCH, Azy), 1 20 (d, 3H, J = 5 7Hz, CH_3) ppm ^{13}C NMR (25 2 MHz in $CDCl_3$) δ 148 5-125 5 (aromatic C), 75 2 and 73 5 (ϕ_3CN and COH alcohol), 45 2 (αCH, MeAzy), 31 9 (βCH, Azy), 13 6 (CH_3, Azy) ppm IR (KBr) υ = 3500 -3300 (OH), 3100-3000, 1600 (aromatic), 3000-2900 (alkyl) cm^{-1}

(+)-3-methyl-(2S,3S)-aziridine-2yl-diphenylmethanol (2a)
Using the same procedure as described for **1a**, compound **14a** (R_1=Me) (7 40 g, 15 3 mmol) was dissolved in a mixture of THF and MeOH (1 1 40 mL) and converted into **2a** using an H_2SO_4 solution (6M, 20 mL) The crude product was purified using flash column chromatography (petroleum ether/ethyl acetate = 3 1) affording 2 62 g (72%) of a white crystalline compound **2a** m p 92 5-93 5°C $[\alpha]^{20}_D$ +82 6° (c=1, $CHCl_3$) Calc for $C_{16}H_{17}NO$ (239 32) C 80 30, H 7 16, N 5 85 %, found C 80 12, H 6 95, N 5 81 % MS (EI) m/e 239 (M^+, 3 6%), 221 (M^+-H_2O, 60 9%), 206 (M^+-H_2O-CH_3, 70 7%), 183 ($(C_6H_5)_2C\text{-}OH^+$, 33 7%), 105 ($C_6H_5CO^+$, 88 7%), 77 ($C_6H_5^+$ 74 1%), 57 (M^+-183, 100%) ^1H NMR (100 MHz in $CDCl_3$), δ 7 46 - 7 06 (m, 10H, aromatic H, phenyl), 2 72(d, 1H, J = 6 0Hz, αCH, Azy), 2 17 (m, 1H, βCH, Azy), 1 00 (d, 3H, J = 6 0Hz, Me) ppm ^{13}C NMR (25 2 MHz in $CDCl_3$), δ 150 0-125 7 (aromatic C), 74 1 ($Ph_2\underline{C}OH$), 42 5 and 31 6 (αCH, Azy and βCH, Azy) 13 6 ($\underline{C}H_3$, Azy) ppm IR (CCl_4) υ = 3500-3300 (OH,NH), 3100-3000, 1600 (aromatic), cm^{-1}

(-)-3-methyl-(2R,3R)-aziridine-2yl-diphenylmethanol (2b)
Using the same procedure as described for **1a**, compound **14b** (R_1=Me) (14 1 g, 29 2 mmol) was dissolved in a mixture of THF and MeOH (1 1, 80 mL) and converted into **11b** using an H_2SO_4 solution (6M, 30 mL) The crude product was purified using flash column chromatography (petroleum ether/ethylacetate = 3 1) affording 5 85 g (83%) of a white crystalline compound **2b** m p 94-95°C $[\alpha]^{20}_D$ -82 8° (c=1, $CHCl_3$) Calc for $C_{16}H_{17}NO$ (239 32) C 80 30, H 7 16, N 5 85 %, found C 80 07, H 6 84, N 5 80 % MS (EI) m/e 239 (M^+, 1 9%), 221 (M^+-H_2O, 61 3%), 206 (M^+-H_2O-CH_3, 76 2%), 183 ($(C_6H_5)_2C\text{-}OH^+$, 35 6%), 105 ($C_6H_5CO^+$, 93 9%), 77 ($C_6H_5^+$, 71 0%), 57 (M^+-183, 100%) ^1H NMR (100 MHz in $CDCl_3$), δ 7 50 - 7 27 (m, 10H, aromatic H, phenyl), 4 65 (s, 1H, OH), 2 84(d, 1H, J = 6 0Hz, αCH, Azy), 2 33 (m, 1H, βCH, Azy), 1 06 (d, 3H, J = 6 0Hz, Me) ppm ^{13}C NMR (25 2 MHz in $CDCl_3$), δ 149 6-126 1 (aromatic C), 73 6 ($Ph_2\underline{C}OH$), 42 5 and 31 6 (αCH, Azy and βCH, Azy) 13 6 ($\underline{C}H_3$, Azy) ppm IR (KBr) υ = 3500-3200 (OH,NH), 3100-3000, 1600 (aromatic), cm^{-1}

General procedure for the reduction of ketones with chiral oxazaborolidines.

Typical procedure for the ketone 17a-e reduction using 10% 1a as the catalyst The reactions were run under an argon atmosphere in a flame dried flask To a solution of **1a** (56mg, 0 25mmol) in THF (10 mL) a BH_3-Me_2S solution in THF (750μL, 2M, 1 5 mmol) was added This solution was heated at reflux temperature for 15 h, followed by removal of the solvent and excess BH_3-Me_2S *in vacuo* THF (3 5 mL) was added to the white solid catalyst, followed by BH_3-Me_2S in THF (1 25 mL, 2M, 2 5 mmol) and the immediate addition of the ketone **17a-e** (2 5 mmol) An exothermic reaction took place After 5 min the ketone **17a-e** had been consumed (TLC) and the reaction was quenched with MeOH (1 25 mL) Dilute sulfuric acid (4 ml, 1M) was added, followed by the removal of the organic solvents *in vacuo* The aqueous residue was extracted with ether (3x) and the collected organic layers were washed with a saturated $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated to give the chiral alcohol **18a-e** in high chemical yields Determination of the enantiomeric excess of alcohol **18a** was performed by GLC (PAS-1701 column 25m) using the camphanoyl derivative of 1-phenylethanol (**18a**) The enantiomeric purity of the products **18a**, **18c**, **18d**, **18e** was determined by HPLC-analysis, using a Chiralcel OD column (flowrate 1 mL/min, eluent **18a,d** 2-propanol/n-hexane =10 90, **18c-e** 2-propanol/n-hexane =2 98) The optical purity of **18b** was determined by measurement of the optical rotation of purified alcohols

Typical procedure for acetophenone reduction using 5% 2a as the catalyst The reactions were run under a nitrogen atmosphere in a flame dried flask To a solution of **2a** (30 mg, 0 125 mmol) in toluene (3 mL) a BH_3-THF solution in THF (250μL, 1M, 0 25 mmol) was added The solution was stirred at room temperature for 10 min Then ketone **17a-e** (2 5 mmol) was added and immediately followed by a BH_3-SMe_2 solution in toluene (1 25 mL, 2 M, 2 5 mmol) An exothermic reaction took place After 30 min the ketone **17a-e** had been consumed (TLC) The reaction

was quenched with MeOH (1 25 mL) Dilute sulfuric acid (4 ml, 1M) was added, followed by the removal of the organic solvents *in vacuo* The aqueous residue was extracted with ether (3x) and the collected organic layers were washed with a saturated $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated to give the chiral alcohol **18a-e** in high chemical yields The optical purities of the chiral alcohols **18a-e** were determined as described above

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4.5 References and Notes

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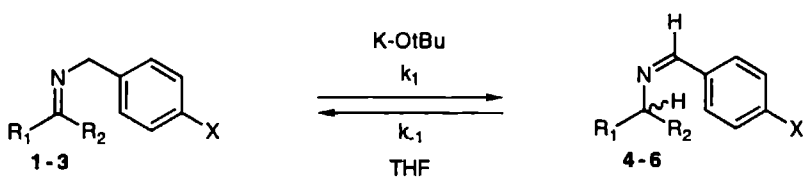
Imine Isomerization Reaction: A Kinetic Study

5.1 Introduction.

Over the years several methods have been developed for the synthesis of amines One of the major routes to amines is based on the heterogeneous or homogeneous metal catalyzed hydrogenation of aldimines and ketimines Another important synthetic approach toward amines is the reductive amination of an aldehyde or ketone, which is also performed on an industrial scale An alternative route toward amines using imine intermediates is the imine isomerization by bases involving an [1,3]-proton shift as depicted in Scheme 5 1 Studies on the mechanism of this imine isomerization reaction (methylene azomethine rearrangement), were performed by Ingold et al [1] in the 1930s, by Ossorio[2] in the 1950s and by Cram et al [3] in the 1960-70s using sodium and potassium alcoholate bases Ingold and Ossorio proposed a one stage concerted mechanism for this imine isomerization reaction Cram and coworkers critisized this one stage mechanism and postulated a two stage imine isomerization process, involving aza-allyl anions as essential reaction intermediates A brief survey on the imine isomerization reaction is given in chapter 2

A study aiming at an asymmetric imine isomerization[4] process (chapter 6) initiated an analysis of the kinetic behavior of the imine model systems **1-3** using achiral bases The kinetic results concerning the [1,3]-proton transfer in the aza-allylic system of N-benzylimines **1-3** catalyzed by K-OtBu, resulting in the formation of thermodynamically favored N-benzylidene derivatives **4-6**, are described in this chapter



1,4 $R_1 = PhCH_2CH_2$, $R_2 = CH_3$
2,5 $R_1 = Ph$, $R_2 = CH_3$
3,6 $R_1 = Ph$, $R_2 = Ph$

X = H (**a**), Cl (**b**), OMe (**c**), CH_3 (**d**), F (**e**)

Scheme 5 1

The imine isomerization reaction can be described by first order equilibrium kinetics From the temperature dependence of the rate of the imine isomerization reaction, the activation energy using the Arrhenius relationship, the overall thermodynamic parameters ΔH, ΔS and ΔG using the standard molar Free Gibbs function, and the energy parameters of activation $\Delta H^{\#}$, $\Delta S^{\#}$ and $\Delta G^{\#}$ using the Eyring relationship were calculated Hammett plots were generated from isomerization data of several *p*-substituted imine model systems **1-3** Important information about the imine isomerization was obtained by monitoring the racemization of the enantiopure product imines **4b**

and **5b**. In the appendix to this chapter a brief outline on first order equilibrium kinetics, and other relevant mechanistic methods is given.

5.2 Results and Discussion

5.2.1 Synthesis and isomerization of imines

For the preparation of imines, starting from their corresponding ketones and amines, several methods are known in the literature. A well known method named after Dean and Stark uses equimolar quantities of amines and ketones and separates the generated water from the reaction mixture by azeotropic distillation.[5] A similar method uses an azeotropic distillation with the addition of Lewis acid catalysts.[6] Other methods are based on the use of water removing agents[7] (molecular sieves or $MgSO_4$) in combination with Lewis acid catalysts,[8] the use of a soxhlet apparatus equipped with a dehydrating agent, or mixing equimolar quantities of amine hydrochlorides and ketones with the addition of Lewis acid catalysts.[9]

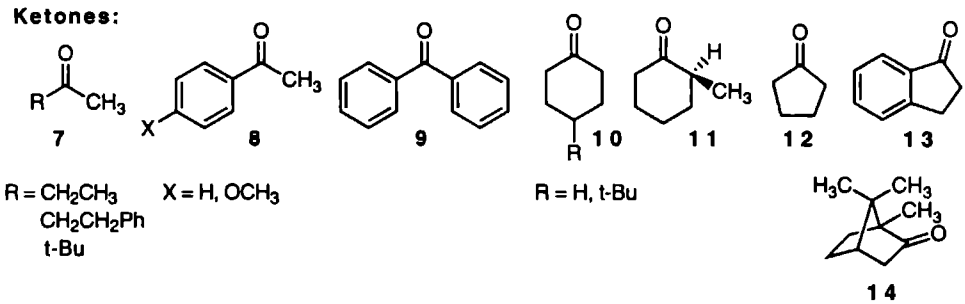


Figure 5.1

Several methods were explored for the synthesis of the imines derived from ketones **7-14** and amines **15-19** using different solvents (Figures 5.1 and 5.2). The purification of the air and moisture sensitive crude imine products turned out to be difficult, due to the fact that most imines were not crystalline. The purification of the oily crude imine reaction products by distillation gave very low yields, due to considerable polymerization and hydrolysis. Initial isomerization experiments revealed that this imine isomerization reaction is extremely sensitive to impurities in the starting imine. Therefore, it was essential to develop an imine synthesis in which the product can be isolated in very high purities (>99%).

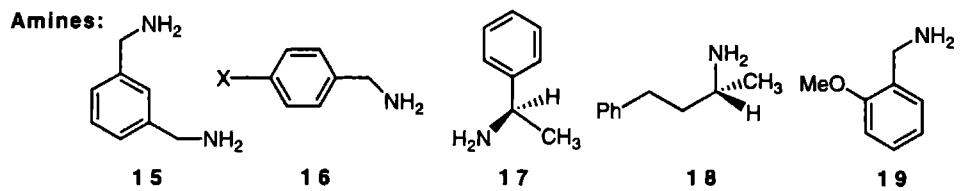


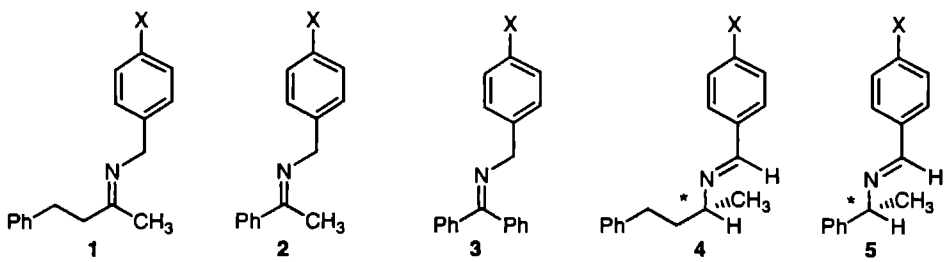
Figure 5.2

A method, in which equimolar amounts of ketone and amine were mixed with a dehydrating agent (molecular sieves or $MgSO_4$) without a solvent at ambient temperature was developed. After 24 h the dehydrating agent was replaced by fresh agent. In most cases three or four changes of dehydrating agent were necessary to obtain the imine product in high yields with a purity higher than 99%. The imines prepared using this method could be stored without decomposition in the refrigerator in the presence of the dehydrating agent for several months.

The isomerization reaction was performed with imines derived from several commercially available aliphatic, cyclic and aromatic ketones **7-14** and aromatic amines **15-16**, and **18-19** If sub-stoichiometric amounts of base (K-OtBu) were used, the isomerization reaction reached equilibrium within 3-6 h , and the equilibrium ratio of the starting material and products was higher than 30 70 in most cases (K_{eq}>2 3) The imines derived from the 5-membered ring ketones cyclopentanone (**12**), indan-1-one (**13**) and sterically crowded R(+)-camphor (**14**), could not be isomerized using K-OtBu as the base When imines derived from acetophenone (**8**, X=H), benzylacetone (**7**, R=CH_2CH_2Ph) and enantiopure R(+)-α-methylbenzylamine (**17**) were used, no isomerization reaction was observed After the addition of the imine derived from **7**, **8** and **17** to a basic solution, the reaction mixture remained colorless, in contrast to the deep red solutions obtained during the isomerization of model imines **1-3** From these observations it was concluded that the imines derived from **17** were not deprotonated under the reactions conditions, which may be due to steric hindrance in the α-methylbenzyl moiety of the imine

5.2.2 Imine model systems

It is of interest to obtain additional information on the mechanism of the imine isomerization reaction and therefore the imines **1-5** were chosen as model systems The kinetic and thermodynamic behavior of model imine systems **1-5** was studied with K-OtBu in THF at different temperatures



Model system **1** is derived from benzylacetone (**7**, R=CH_2CH_2Ph) and *p*-X-benzylamine (**16**), and was also studied in the asymmetric isomerization (chapter 6) The imines derived from **7** and **16** were not crystalline, except for the *p*-Cl benzylamine derivative **1b**, and were prepared using solvent free reaction conditions Model system **2** is derived from acetophenone (**8**, X=H) and *p*-X-benzylamine (**16**), and is, being a prochiral imine, also suitable as a model system in catalytic asymmetric imine isomerization reactions Model imine **3**, derived from benzophenone (**9**) and *p*-X-benzylamine (**16**) was analyzed in order to compare its kinetic behavior with that of the non-conjugated imine **1**, and the mono-phenyl conjugated imine **2** Model imine **3** is not prochiral, and therefore cannot be used as substrate in the asymmetric isomerization reaction Model imines **2** and **3** were prepared using Dean Stark reaction conditions with the addition of BF_3-OEt_2 as the Lewis acid catalyst, followed by several recrystallizations from EtOH With this procedure crystalline imines **2** and **3** were obtained in high purity (>99 5%) but in moderate yields (25-45%)

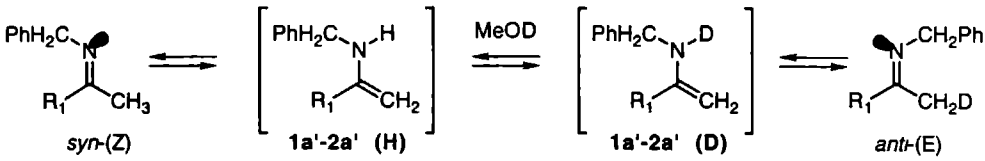
In order to obtain insight in the reverse imine isomerization reaction and the rate of racemization of (**4**<=>**1**) and (**5**<=>**2**), the product imines **4** and **5** were prepared, using *p*-substituted aldehydes and enantiopure chiral amines R(+)-α-methylbenzylamine (**17**) and R(+)-4-phenyl-amino-2-butane (**18**), respectively The synthesis of imines derived from aldehydes could be performed with relative ease, using equimolar amounts of amine and aldehyde in the presence of a dehydrating agent (mol sieves 3Å or $MgSO_4$) In most cases only one replacement of fresh dehydrating agent is necessary to obtain the imines in high yields and high purity

Preliminary isomerization experiments of model imine **1a** and **1b** using several different achiral bases, DBU,[10] DABCO,[11] DBU/LiBr,[12] and LDA[13] in different solvents such as t-BuOH, DME and THF were not successful In some cases deprotonation of the imine occurred, visible by the formation of a deep red colored solution, but no imine isomerization took place However, K-OtBu was able to catalyze the imine isomerization reaction of **1a-b** into **4a-b** in THF at room temperature When Li^+ and Na^+ were used in stead of K^+ counterions no imine isomerization of imines **1a-b** was observed Model imines **2a** and **3a** gave fast imine isomerization reactions at room temperature when K-OtBu in THF was applied The catalytic abilities of the bases Li-OtBu and Na-OtBu in THF were not studied for model imines **2a** and **3a**

The imine isomerization reactions were performed under Schlenk conditions, in view of the high moisture sensitivity of the imine model systems The glassware was flame dried under vacuum and all reactions were run in an argon atmosphere The conversion of the starting imine into the product was monitored using gas chromatography The reaction conditions were chosen such that the rate of conversion was slow and the product formation could be analyzed manually Kinetics using model imine **1b** were performed in the temperature range of 22-66°C Model imines **2a** and **3a** could not be analyzed at these temperatures, because at these temperatures equilibrium was reached very fast Therefore, it was decided to use lower temperatures (-52)-(-10)°C The rate and equilibrium constants of the isomerization reactions of model imines **1-3** and **4-5** could be determined The reactions could be described by first order equilibrium kinetics and the rate constants of the forward (k_1) and reverse (k_{-1}) reactions as well as the equilibrium constants (K_{eq}) at different temperatures could be determined

5.2.3 NMR experiments using model imines 1 and 2

Imines **1a** and **2a** are in tautomeric equilibrium with their secondary enamine forms **1a'** and **2a'** [14] This equilibrium is almost completely in favor of the imine forms **1a** and **2a**, except when the enamine form is stabilized by further conjugation This has been established by spectroscopic studies of **1a** and **2a**, including ^1H NMR, H/D exchange of the α,α' protons in MeOD [15] The *syn/anti* (E/Z) isomerization of imine **2a**-(Z) is proposed to proceed through the tautomeric secondary enamine **2a'** For the E/Z isomerization of imines **1a** a similar mechanism is proposed



1a $R_1 = PhCH_2CH_2$
2a $R_1 = Ph$

Scheme 5 2

Additional information on the isomerization reaction of imine **1a-b** into **4a-b** and **2a** into **5a** was obtained by recording the ^1H and ^{13}C-NMR spectra during the reaction These experiments were performed in an NMR-tube under Schlenk reaction conditions using freshly distilled TDF and a sub-stoichiometric amount of sublimed K-OtBu. After the addition of the imine substrate an intense dark red color developed The conversion of imines **1a-b** (X = H and Cl) into **4a-b** and **2a** into **5a** was monitored using several proton signals of the respective imines From the intensity of the benzylic CH_2 signals the ratio of the *syn/anti* (*E/Z*) isomers was calculated to be 1 4 for **1a-b** and 1 12 for **2a** The proton signals used to determine the conversion ratio of imine **1a-b** into **4a-b** and **2a** into **5a** are depicted in Figure 5 3 No anionic species could be detected in the NMR spectrum for the reaction of **1a-b** into **4a-b** and **2a** into **5a**, although a substoichiometric amount of K-OtBu was employed The results obtained reveal that the

concentration of the reactive intermediate in the imine isomerization is relatively low. An additional indication for this low intermediate concentration was obtained from the absence of peak broadening of the proton signals in the NMR spectra and the absence of the characteristic aza-allyl anion 'fingerprint' in the NMR spectrum as described by Andrews et al.[16]

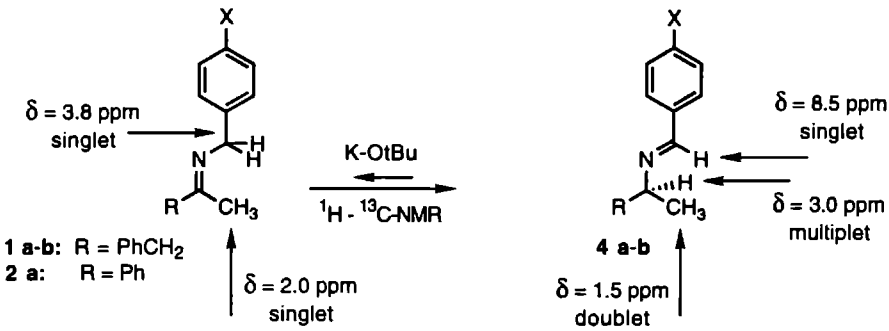


Figure 5.3

5.2.4 Isomerization kinetics of model imines 1, 2 and 3

For the Eyring- and Arrhenius analysis imine **1b** (X = Cl) was used, because this model imine is crystalline and could be obtained in pure form by crystallization. Imines **2a** (X=H) and **3a** (X=H), which are both crystalline and could be obtained in high purities, were chosen as the other model systems in the kinetic study of the imine isomerization reaction. The reaction was described using pseudo first order equilibrium kinetics, and the base concentration, which is constant during the reaction, is part of the calculated reaction constants k_1 and k_{-1}.

The dependence of the rate of isomerization of model system **1b** on the catalyst concentration was investigated. Compound **1b** was converted into **4b** using an imine concentration of 0.1 mmol/mL and the base concentration (K-OtBu) was varied from 0.2 to 2.0 equivalents. The isomerization reactions were performed at room temperature.

Table 5.1 Rate constants of model imine **1b** (X=Cl) at different K-OtBu concentrations.

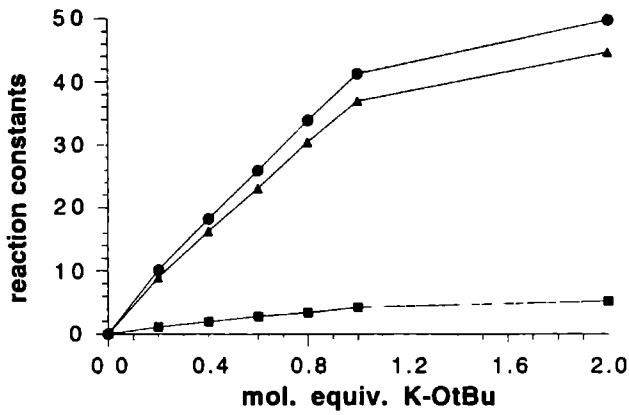
Entry	Mol equiv. K-OtBu	K_{eq}	k_1 (10^{-3} min^{-1})	k_{-1} (10^{-3} min^{-1})	k_{exp} (10^{-3} min^{-1})
1	0.2	8.22	8.96	1.09	10.1
2	0.4	8.31	16.2	1.95	18.2
3	0.6	8.19	23.1	2.82	25.9
4	0.8	8.99	30.4	3.38	33.8
5	1.0	8.66	36.9	4.26	41.2
6	2.0	8.68	44.6	5.14	49.7

a) k_{exp} and K_{eq} were determined from a plot of $[A_t]/[A_0]$ against time. b) $k_{exp} = k_1 + k_{-1}$, as derived in the appendix.

The imine isomerization was followed by monitoring the disappearance of the starting imine **1b** and the appearance of the product imine **4b** as a function of time using capillary GLC. Since both imines **1b** and **4b** have the same molecular weight, it was assumed that the conversion could be determined directly from the GLC chromatogram, without the use of an internal standard. The kinetic results are collected in Table 5.1. Isomerization experiments using varying amounts of base catalyst show that if catalytic amounts of base are present ([base] = 0.2-1.0 equiv.) the reaction is

first order in base. In the presence of more than 1.0 equiv. of catalyst, the reaction is no longer first order in base. (Figure 5.4).

Figure 5.4 Base concentration dependence of the isomerization of imine **1b**.



● = k_{exp}, ▲ = k_1, ■ = k_{-1}

At high base concentrations ([K-OtBu >2 0 equiv.), the reaction mixture became heterogeneous, because of the limited solubility of K-OtBu in THF, which explains the deviation from the first order kinetics.

Table 5.2 Kinetic data for the isomerization of model imine **1b** at different temperatures.

Entry	Temperature °C	K_{eq}	k_1 (10^{-3} min^{-1})	k_{-1} (10^{-3} min^{-1})	k_{exp} (10^{-3} min^{-1})
1	22	8.19	23.1	2 82	25 9
2	34	7 57	54.5	7 2	61 7
3	43	7.03	67.5	9 6	77.1
4	66	5.36	252.5	47.1	299 6

a) [imine **1b**] = 0 1 mmol/mL b) [base] = 0 6 equivalent (0 06 mmol/mL) c) $k_{exp} = k_1 + k_{-1}$ (see appendix)

For model imines **2a** and **3a** it was assumed that the isomerization reaction was also first order in base, when catalytic amounts of K-OtBu are employed. For these imines no base concentration dependence experiments were performed.

Table 5.3 Kinetic data for the isomerization of model imine **2a** at different temperatures

Entry	Temperature °C (K)	K_{eq}	k_1 (10^{-3} min^{-1})	k_{-1} (10^{-3} min^{-1})	k_{exp} (10^{-3} min^{-1})
1	-40 (233)	3.34	4.81	1 44	6.25
2	-30 (243)	3.15	21.2	6.72	27 9
3	-18 (255)	2.93	87.2	29.8	117 0
4	-10 (263)	2.63	208.8	79 4	288 2

a) [imine **2a**] = 0 05 mmol/mL b) [base] = 0 3 equivalent (0 015 mmol/mL) c) $k_{exp} = k_1 + k_{-1}$ (see appendix)

The kinetic data for model imines **1b**, **2a**, and **3a** at different reaction temperatures are collected in Tables 5.2, 5.3, and 5.4, respectively. To determine the Eyring, Arrhenius, and Gibbs parameters of the imine isomerization reaction, the concentration of model imine **1b** was fixed at 0.1 mmol/mL with a base concentration of 0.6 equivalents and the reaction was performed in the temperature range of 22-66°C. Model imines **2a** and **3a** were analyzed at an imine concentration of 0.05 mmol/mL using a base concentration of 0.3 equivalents. All isomerization reactions were performed in freshly distilled THF under Schlenk conditions.

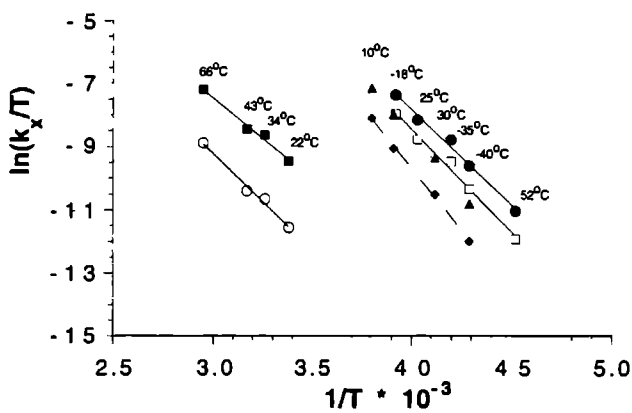
Table 5.4 Kinetic data for the isomerization of model imine **3a** at different temperatures.

Entry	Temperature °C (K)	K_{eq}	k_1 (10^{-3} min^{-1})	k_{-1} (10^{-3} min^{-1})	k_{exp} (10^{-3} min^{-1})
1	-52 (221)	2.45	3.60	1 47	5 07
2	-40 (233)	2 10	15.8	7.52	23 3
3	-35 (238)	2.02	37.1	18.4	55.5
4	-25 (248)	1.88	72 2	38.4	110.6
5	-18 (255)	1.81	161.4	89.2	250.6

a) [imine **3a**] = 0 05 mmol/mL b) [base] = 0 3 equivalent (0 015 mmol/mL) c) $k_{exp} = k_1 + k_{-1}$ (see appendix)

The results show that the imine isomerization reaction is faster at higher temperatures, whereas the equilibrium constant (K_{eq}) is lowered when the temperature is increased. The accuracy of the values of the reaction rate constants calculated for model imines **1a-e** was determined by comparison of the results of three experiments and a standard deviation of ca. 5% was found in the data. Data acquisition was performed manually during the imine isomerization experiments and reactions with rate constants larger than 350×10^{-3} min^{-1} could not monitored by this procedure. The reason for this limit is that isomerization reactions with rate constants higher than 350×10^{-3} min^{-1} reach equilibrium within 2 min., and in this short period of time a limited number of data points can be obtained by the manual sampling technique.

Figure 5.5 Eyring relationship of model imines **1b**, **2a** and **3a**

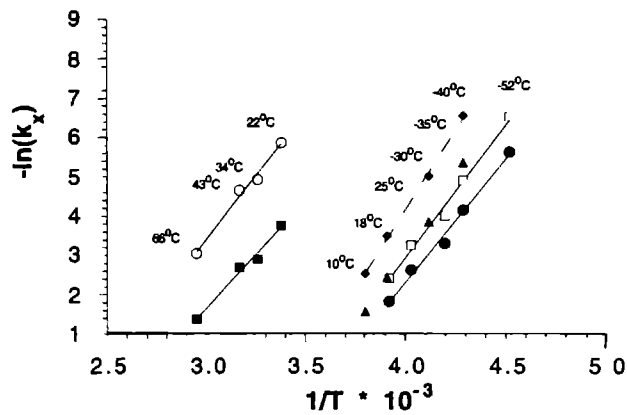


○ ln(k$_{-1}$/T)-imine (**1b**), ■ = ln(k$_1$/T) imine (**1b**), ◆ = ln(k$_{-1}$/T)-imine (**2a**), ▲ = ln(k$_1$/T)-imine (**2a**), □ = ln(k$_{-1}$/T)-imine (**3a**), ● = ln(k$_1$/T)-imine (**3a**)

The relatively low reaction temperatures [(-52)-(-10)°C] applied during the kinetic experiments with imines **2a** and **3a** caused problems in the case of THF as the solvent. Even under rigorous exclusion of water and air, using Schlenk conditions and a continuous argon

pressure, the solvent attracted water (T< -25°C). This problem was caused by the sampling method, in which syringes with metal syringe needles were used repeatedly to withdraw aliquots from the reaction mixture. The presence of water during the imine isomerization induces imine hydrolysis and catalyst degradation, which has a negative effect on the accuracy of the kinetic results In most cases, the accuracy of the rate constants measured at low temperatures was decreased (ca. 10%) as compared to the data obtained for model imine **1b** (accuracy is ca. 5%) in the temperature range of 22 to 66°C.

Figure 5.6 Arrhenius relationship for model imines **1b**, **2a** and **3a**.



○ ln(k$_{-1}$)-imine (**1b**), ■ = ln(k$_1$)-imine (**1b**), ◆ = ln(k$_{-1}$)-imine (**2a**), ▲ = ln(k$_1$)-imine (**2a**), □ = ln(k$_{-1}$)-imine (**3a**), ● = ln(k$_1$)-imine (**3a**)

The Eyring and Arrhenius relationships derived from the experiments at different temperatures with imines **1b**, **2a** and **3a** for the forward (k$_1$) and the reverse (k$_{-1}$) reactions are shown in Figures 5.5 and 5.6. According to equation A.19 (appendix) the slopes of the lines in Figure 5.5 equal to $\Delta H^{\#}/R$ and the intercepts to $\Delta S^{\#}/R + \ln(k_B/h)$ where R, k_B and h, are the gas constant, the Boltzmann constant and the Plancks constant, respectively. From $\Delta H^{\#}$ and $\Delta S^{\#}$ the value of $\Delta G^{\#}$ can be calculated using equation A.13 (appendix). The parameters $\Delta G^{\#}$, $\Delta H^{\#}$, $\Delta S^{\#}$, E_a, thus derived are collected in Table 5.5. According to equation A.17 (appendix) the slopes of the lines in Figure 5.6 equal to E_a/R and the activation energy (E_a) can be calculated Extrapolation of the Arrhenius plots for the model imines **1b**, **2a** and **3a** to -40°C was performed, taking into consideration the difference in base concentration (0.6 in stead of 0.3 equivalents) as well as the presence of the *p*-Cl substituent for imine **1b**.

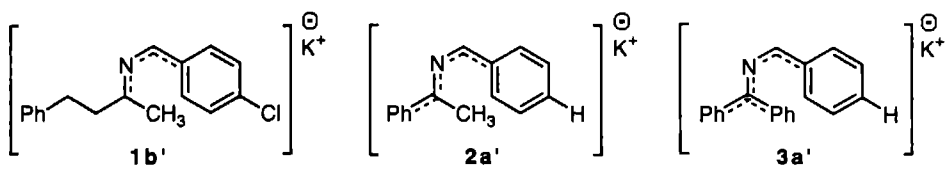


Figure 5.7

The relative reaction rates of the model imines **1b**, **2a** and **3a** could be determined as **1b** **2a** **3a** = 1 · 115 : 405. The difference in reaction rates can be explained when the stability of the three aza-allyl anions **1b'**, **2a'** and **3a'** is considered (Figure 5.7). The aza-allyl anions of imines **1b**, **2a** and **3a** are stabilized by one, two and three phenyl rings, respectively, and the best

stabilized aza-allyl anion will be obtained by deprotonation of imine **3a**. The $\Delta G^{\#}$ values (298K) for model imines **2a** and **3a** are in the same range ($\Delta G^{\#}$ = 67-70 kJ/mol) and the lower reaction rate constants of the isomerization of model imine **1b** are reflected by higher values of $\Delta G^{\#}$ ($\Delta G^{\#}$ = 81-87 kJ/mol). The relatively small difference in $\Delta G^{\#}$-values for imines **2a** and **3a** may be explained by steric interactions of the benzophenone phenyl-groups in the anion derived from **3a** as compared to the acetophenone phenyl group in **2a'**. Presumably, these steric interactions require that one or both phenyl groups in anion **3a'** are out of plane of the C=N-C-anion system, which will induce a decrease in the resonance stabilization of the phenyl groups in this intermediate. A similar behavior associated with this second phenyl ring in benzophenone derived imines as compared to benzaldehyde derived imines was observed by O'Donnel et al.[17] in a study concerning the acidity of glycine Schiff bases.

A difference in the free energy of activation [$\Delta G^{\#}(298)$] of ca.15 kJ/mol is observed for imine **1b** in comparison with **2a** and **3a** and from this difference a reduction of the reaction rate of a factor of 1000 can be calculated. The relative reaction rates of the model imines **1b**, **2a** and **3a** at T=25°C were determined as 1 : 850 : 915, which is in agreement with the measured difference in the free energy of activation ($\Delta G^{\#}$).

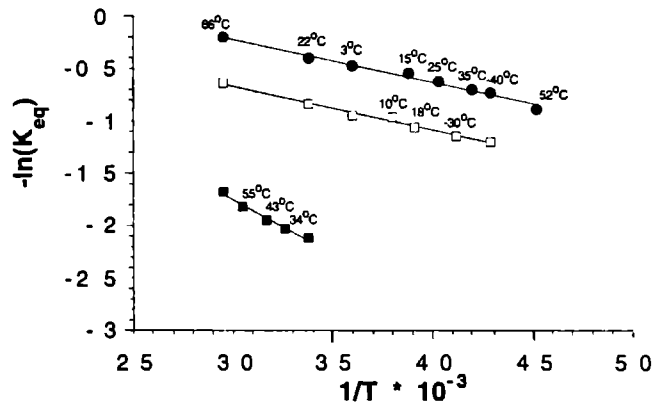
Table 5.5 Results obtained from the Eyring and Arrhenius analyses of the rate constants for imines **1b**, **2a**, **3a**

Entry (imine)	Reaction constant	Temp. range (°C)	E_a (kJ mol^{-1})	$\Delta G^{\#}$ (kJ mol^{-1}) (298K)	$\Delta H^{\#}$ (kJ mol^{-1})	$\Delta S^{\#}$ (J mol^{-1} K^{-1})
1 (**1b**)	k_{exp}	(22)-(66)	46.0	+81.6	+43.5	-127.9
2 (**1b**)	k_1	(22)-(66)	44.9	+81.9	+42.4	-132.6
3 (**1b**)	k_{-1}	(22)-(66)	53.2	+87.1	+50.7	-122.1
4 (**2a**)	k_{exp}	(-40)-(-10)	63.9	+67.6	+61.8	-19.5
5 (**2a**)	k_1	(-40)-(-10)	62.9	+68.5	+60.8	-25.8
6 (**2a**)	k_{-1}	(-40)-(-10)	66.8	+70.5	+64.7	-19.4
7 (**3a**)	k_{exp}	(-52)-(-18)	53.3	+67.3	+51.4	-53.3
8 (**3a**)	k_1	(-52)-(-18)	51.9	+68.6	+49.9	-62.9
9 (**3a**)	k_{-1}	(-52)-(-18)	56.0	+69.4	+54.0	-51.7

As shown in Table 5.5 the entropies of activation for the model imines **1b**, **2a** and **3a** are negative. Imine **1b** has the most negative entropy of activation [$\Delta S^{\#}$ = (-122)-(-132) J/mol/K] which points to a highly ordered, rigid transition state in the isomerization reaction. For model imines **2a** and **3a** the entropies of activation are much smaller, *viz.* $\Delta S^{\#}$ = (-19)-(-26) J/mol/K and $\Delta S^{\#}$ = (-51)-(-62) J/mol/K, respectively. A highly negative entropy of activation is expected when aza-allyl anions play an important role during the imine isomerization reaction. Aza-allyl anions are rigid and will be relatively inflexible, due to the conjugation present in these reactive intermediates. The reason for the difference in the entropies of activation of model imines **1b**, **2a** and **3a** may be explained by comparing the flexibility of starting imines **1b**, **2a** and **3a** with the the reactive intermediates **1b'**, **2a'** and **3a'** (Figure 5.7) derived therefrom. Imine **1b** is highly flexible and is in tautomeric equilibrium with two possible enamines. The conversion of **1b** into the rigid aza-allyl anion **1b'** will occur with a relatively high negative entropy change. Imines **2a** and **3a** are less flexible in comparison with imine **1b**. Imine **2a** is in tautomeric equilibrium with only one enamine structure. For imine **3a** no tautomeric equilibrium with enamines is possible, due to the lack of α-hydrogen atoms in this model system. Therefore, for the deprotonation of imines **2a** and **3a**, the entropy change is expected to be lower than for imine **1b**. Furthermore, a negative entropy

change is expected if anions play an important role as intermediates due to a higher ordering of the solvent molecules in the polar transition state This solvent induced contribution to the entropy change is expected to have almost equal values for imines **1b**, **2a** and **3a** From the equilibrium constants at different temperatures as shown in Tables 5.2, 5 3 and 5 4 a Gibbs relationship for model imines **1b**, **2a** and **3a** can be derived Gibbs plots give access to ΔG, ΔH, and ΔS values of the overall imine isomerization reaction The Gibbs plots of model imines **1b** (X = Cl) , **2a** and **3a** (X = H) are depicted in Figure 5 8 A relatively large negative value for ΔG (ΔG=-5 25 kJ/mol) is obtained for model imine **1b**

Figure 5.8 Gibbs relationship of model imines **1b**, **2a** and **3a**



■ $ln(K_{eq})$-imine (**1b**), ● = $ln(K_{eq})$-imine (**2a**), □ = $ln(K_{eq})$-imine (**3a**)

This is in accordance with the expectation because a non-conjugated imine is converted into a thermodynamically favored conjugated double bond For model imines **1b**, **2a** and **3a** negative values of ΔS are obtained The absolute value of the overall entropy change during the isomerization reaction of imine **1b** (ΔS=-10 7 J/K/mol) is higher than the ΔS-values obtained for imines **2a** and **3a** This can be explained by taking the number of enamine tautomers of model imine **1b** in comparison with the product imine **4b** into account (Figure 5 9)

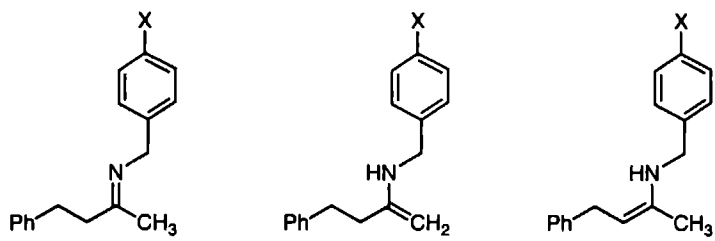


Figure 5 9

The starting imine **1b** can exist in the *syn/anti* form and can equilibrate with two enamine tautomers of which one shows cis/trans isomerism. Product imine **4b** only occurs as *syn/anti* isomers, however, it was shown by ^{1}H-NMR that the *anti* isomer predominates in solution completely The difference in the number of possible equilibrating isomers of starting material versus product gives rise to the negative value of the entropy change during the isomerization reaction

5.2.5 Substituent effects

To establish the effect of substituents in the benzyl group on the imine isomerization several *p*-substituted imines, *viz* **1a-e**, **2a-e** and **3a-e** were prepared and their thermodynamic parameters were determined in a similar manner as described above. The data for **1a-e**, **2a-e** and **3a-e** are collected in Tables 5.6, 5.7, 5.8 and 5.9. These data reveal that the overall entropy change during the isomerization reaction of the *p*-substituted model imines **2a-e** have similar values, *viz.* in the range of -3.03 and -4.94, which those for **3a-e** are in the range of -7.52 and -8.70 J $mol^{-1}K^{-1}$. Therefore, the difference in equilibrium of the *p*-substituted imine model systems **2a-e** and **3a-e** is determined by the overall enthalpy change during the isomerization process and influenced by the *p*-substituent present in the modelsystem in a large extent.

Table 5.6 Thermodynamic parameters derived from Gibbs plots for imines **1b**, **2a-e**, **3a-e**

Entry (imine)	X	temp. range (°C)	K_{eq}[a] (298K)	ΔG (kJ mol^{-1}) (298K)	ΔH (kJ mol^{-1})	ΔS (J mol^{-1} K^{-1})
1 (**1b**)	Cl	(22)-(66)	8.32	-5.25	-8.43	-10.7
2 (**2a**)	H	(-40)-(66)	2.27	-2.03	-3.50	-4.94
3 (**2b**)	Cl	(-40)-(66)	1.36	-0.75	-1.66	-3.06
4 (**2c**)	OMe	(-40)-(66)	9.05	-5.46	-6.36	-3.03
5 (**2e**)	F	(-40)-(66)	2.26	-2.02	-3.08	-3.57
6 (**3a**)	H	(-52)-(66)	1.45	-0.92	-3.42	-8.40
7 (**3b**)	Cl	(-40)-(66)	1.19	-0.42	-2.66	-7.52
8 (**3c**)	OMe	(-40)-(66)	2.61	-2.38	-4.78	-8.06
9 (**3e**)	F	(-40)-(66)	1.59	-1.15	-3.74	-8.70

a) K_{eq} values (298K) determined using Gibbs-plots.

The kinetic data show that the equilibrium constants (K_{eq}) for model imines **1a-e** are not influenced to a great extent by the respective substituents, whereas for model imines **2a-e** and **3a-e** a somewhat larger difference in K_{eq}-values for the respective *p*-substituted substrates is observed. A probable explanation for the rather moderate effect of the *p*-substituents for **1a-e** on the K_{eq}-values is that the equilibrium of the reaction will be mainly determined by the formation of conjugated product imines **4a-e** starting from a non-conjugated compound **1a-e**.

Table 5.7 Imine isomerization kinetics of *p*-substituted model imines **1a-e**.

X=	Temperature °C (K)	K_{eq}	k_1 (10^{-3} min^{-1})	k_{-1} (10^{-3} min^{-1})	k_{exp} (10^{-3} min^{-1})
H	22 (296)	9.48	14.5	1.53	16.0
Cl	22 (296)	8.19	23.1	2.82	25.9
OMe	22 (296)	13.3	3.07	0.23	3.30
Me	22 (296)	12.2	9.98	0.82	10.8
F	22 (296)	9.17	8.80	0.96	9.76

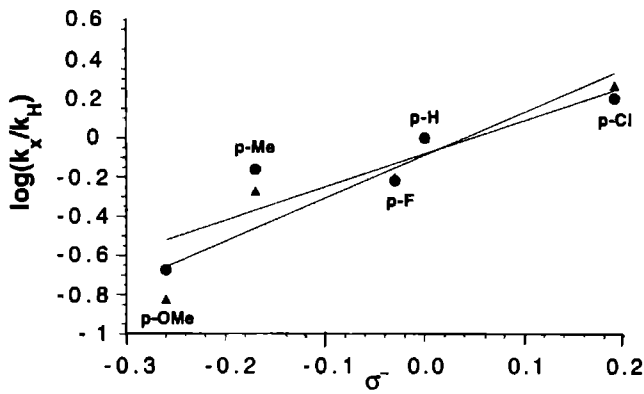
a) All k-values are the average of two experiments. b) Standard deviation = ca. 5 %. c) k_{exp} and K_{eq} were determined from a plot of $[A_t]/[A_0]$ against time. d) $k_{exp} = k_1 + k_{-1}$, as derived in the appendix.

For imines **2a-e** and **3a-e** the starting material as well as the products **5a-e** and **6a-e** possess a conjugated imine double bond and therefore the *p*-substituent and the thermodynamic

stability of the product as compared to the starting material is lower and more dependent on the *p*-substituent.

The rate of isomerization (k_{exp}) of model imines **1a-e** increases for electron-withdrawing substituents (*p*-Cl), and decreases for electron-donating substituents (*p*-OMe). This behavior is expected for a reaction involving negatively charged aza-allyl anions as intermediates, because delocalization of negative charge is facilitated by electron-withdrawing substituents and hampered by electron-donating groups. The Hammett plots for the forward (k_1) and reverse (k_{-1}) reactions of model imine **1a-e** are depicted in Figure 5.10. The best linear Hammett relationship was obtained when σ^- substituent constants were used, which is indicative of the presence of aza-allyl anion intermediates driving the imine isomerization reaction. The Hammett plots show that the reaction constants (ρ) for both the forward reaction and reverse reaction have positive values, *viz.* +1.70 and +2.20, respectively. The correlation coefficients (R) are 0.90 and 0.94, respectively. In the case of a concerted mechanism lower values for the reaction constants would be expected. Furthermore, it is clear that both the forward (k_1) and the reverse (k_{-1}) isomerization rates are increased by electron-withdrawing substituents.

Figure 5.10 Hammett plots for model imines **1a-e**



● = log (k_{1X} / k_{1H}) and ▲ = log (k_{-1X} / k_{-1H}). Reaction conditions: [imine] = 0.1 mol/l and [k-OtBu] = 0.6 equiv.

The Hammett plots for the forward (k_1) and reverse (k_{-1}) isomerization reaction of model imines **2a-e** are depicted in Figure 5.11. For this imine system a different substituent dependence is observed. Instead of the expected rate increase of the forward isomerization (k_1) in the presence of electron-withdrawing groups, the substituent behavior is reversed.

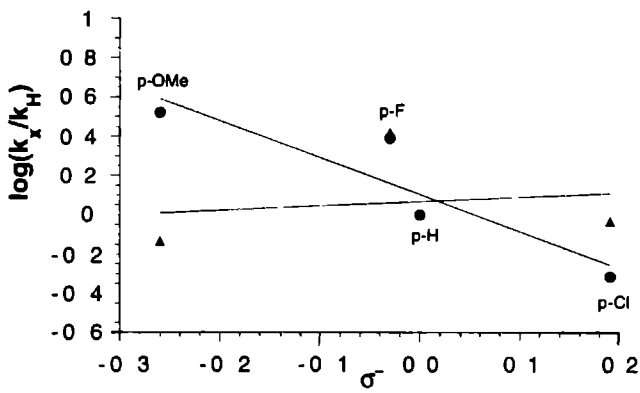
Table 5.8 Imine isomerization kinetics of *p*-substituted model imines **2a-e**.

X=	Temperature °C (K)	K_{eq}	k_1 (10^{-3} min^{-1})	k_{-1} (10^{-3} min^{-1})	k_{exp} (10^{-3} min^{-1})
H	-18 (255)	2.93	87.2	29.8	117.0
Cl	-18 (255)	1.53	42.2	27.6	69.8
OMe	-18 (255)	13.2	288.6	21.9	310.5
F	-18 (255)	2.74	213.6	78.0	291.6

a) All k-values are the average of two experiments. b) Standard deviation = ca. 10%. c) k_{exp} and K_{eq} were determined from a plot of $[A_t]/[A_0]$ against time. d) $k_{exp} = k_1 + k_{-1}$, as derived in the appendix.

With electron-donating substituents an increase in the forward reaction rate (k_1) is observed, whereas electron-withdrawing substituents slow down this isomerization reaction. In the case of the reverse imine isomerization only a small substituent dependence is observed The Hammett plots show that the reaction constant (ρ) for the forward reaction is negative (ρ = -1 88) and for the reverse reaction a value of + 0 22 is observed The correlation coefficients are 0 91 and 0 75, respectively From the high Hammett ρ-value for the forward isomerization reaction it can be concluded that aza-allyl anions are the essential intermediates in these reactions. The fact that the ρ-value for the forward reaction is negative, which usually is an indication for the presence of cationic intermediates, is explained below In a process in which negatively charged aza-allyl anions play an important role (model imine **1a-e**), a positive ρ-value indicates that the deprotonation is the rate determining reaction step If the deprotonation were rate determining, an electron-withdrawing *p*-substituent (*p*-Cl) will result in an increase of the reaction rate, because of the higher stability of the intermediate aza-allyl anion

Figure 5.11 Hammett plots for model imines **2a-e**



● = log (k_{1X} / k_{1H}) and ▲ = log (k_{-1X} / k_{-1H}) Reaction conditions [imine] = 0 05 mol/l and [k-OtBu] = 0 3 equiv

For model imines **2a-e** a different behavior was observed which is explained by a different rate determining step in the isomerization reactions of imines **1a-e** as compared with **2a-e** In the forward imine isomerization of imines **2a-e** the protonation of the aza-allyl anion intermediate (**2'a-e**) is expected to be rate determinating An increase in the overall isomerization reaction rate is observed when an electron-donating substituent (*p*-OMe) is present. The anionic carbon will have a higher electron density, which facilitates the protonation step and a faster imine isomerization reaction will result The reason for the low substituent dependence for the reverse imine isomerization process, can be explained by assuming only a marginal difference in the rate of protonation and deprotonation

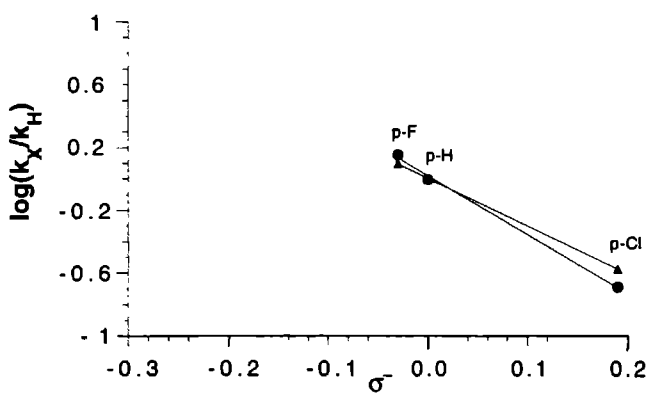
Table 5.9 Imine isomerization kinetics of *p*-substituted model imines **3a-e**.

X=	Temperature °C (K)	K_{eq}	k_1 (10^{-3} min^{-1})	k_{-1} (10^{-3} min^{-1})	k_{exp} (10^{-3} min^{-1})
H	-40 (233)	2.10	15.8	7.52	23.3
Cl	-40 (233)	1.60	3.24	2.02	5.26
OMe	-40 (233)	4.46	9.97	2.23	12.2
Me	-40 (233)	--	--	--	--
F	-40 (233)	2.38	22.6	9.49	32.1

a) All k-values are the average of two experiments. b) Standard deviation = ca. 10%. c) k_{exp} and K_{eq} were determined from a plot of $[A_t]/[A_0]$ against time. d) $k_{exp} = k_1 + k_{-1}$, as derived in the appendix.

The Hammett plots for the forward and reverse isomerization reaction of imines **3a-e** are depicted in Figure 5.12. The Hammett plots show negative ρ-values for both the forward (k_1) and reverse reaction (k_{-1}) and have values of -3.8 and -3.0, respectively. The data for the *p*-OMe substituent are not included in this Hammett analysis because of the low reproducibility with this model system. Low rate constants were observed for this model imine and in most cases equilibrium was not reached at the temperature applied (-40°C). The correlation coefficient (R) amounts 0.99 for the Hammett plots shown. No data for the *p*-Me substituted imine could be obtained, because this imine could not be isolated in crystalline form at room temperature. In experiments using oily *p*-Me substituted imine substrate, no isomerization occurred upon addition of K-OtBu. During these experiments the characteristic deep red color of aza-allyl anions in THF was not observed, which may be due to the presence of water in the imine sample.

Figure 5.12 Hammett plot of model imines **3a-e**



● = log (k_{1X} / k_{1H}) and ▲ = log (k_{-1X} / k_{-1H}). Reaction conditions: [imine] = 0.05 mol/l and [k-OtBu] = 0.3 equiv.

The Hammett plots for model imines **3a-e** reveal that electron-donating substituents increase the reaction rate and electron-withdrawing substituents slow down the forward isomerization reaction. These results show a reversal in behavior as compared with the Hammett results for model imine **1a-e**. From the high Hammett reaction constant values (ρ) for the forward imine isomerization reaction it can be concluded that aza-allyl anions are the essential intermediates in the isomerization reactions. The fact that the Hammett reaction constants (ρ) for the forward as well as the reverse reaction have negative values, instead of positive values as found for model imine **1a-**

e, may be explained by a difference in the rate determining step as going from **1a-e** to **2a-e** and **3a-e**. With the results obtained in the Eyring, Arrhenius, Gibbs and Hammett analyses energy profiles for the imine isomerization reaction of **1b**, **2a** and **3a** can be drawn (Figures 5.13, 5.14 and 5.15). The energy difference ($\Delta\Delta G^{\#}$) between the transitions states $A^{\#}$ and $B^{\#}$ for imine model systems **1b**, **2a** and **3a** was calculated to be 0.05, 0.03 and 0.12 kJ/mol, respectively.

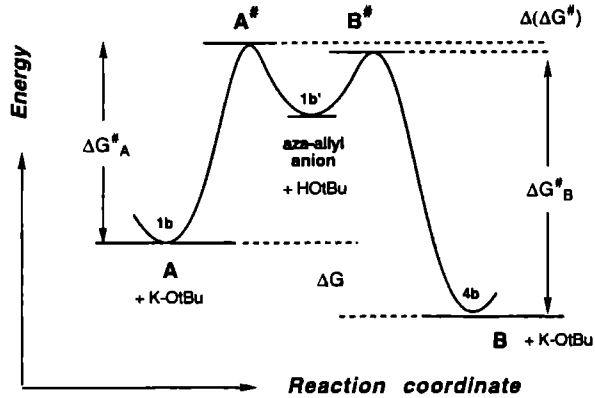


Figure 5.13

The large differences in the kinetic behavior of *p*-substituted model imines **1b**, **2a** and **3a**, especially regarding the Hammett results, can not be explained by the small difference in $\Delta\Delta G^{\#}$-values that were calculated for the model imines **1b**, **2a** and **3a**. A possible explanation for the observed phenomena is the following. For the forward isomerization of model imines (**1b<=>4b**) as well as the reverse isomerization (**4b<=>1b**) electron-withdrawing substituents (*p*-Cl) increase the reaction rate.

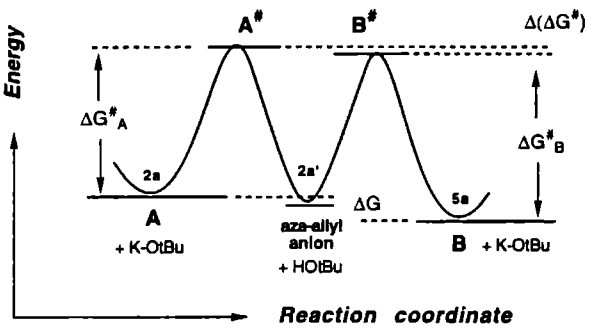


Figure 5.14

The first step in the isomerization is the deprotonation of the imines **1b** and **4b** and for deprotonation to occur the $\Delta G^{\#}_A$ and $\Delta G^{\#}_B$-values of 81.9 and 87.1 kJ/mol have to be overcome. In the presence of an electron-withdrawing substituent, the imine isomerization reaction rate will increase only if the deprotonation of the starting imine is rate determinating and the aza-allyl anion is better stabilized. Due to the fact that the aza-allyl anion intermediate is stabilized by only one phenyl group, this intermediate will have a relatively high energy level and the deprotonation of both imines **1b** and **4b** is expected to be rate determining as shown in Figure 5.13.

A different *p*-substituent behavior was monitored for the isomerization of imines (**2a<=>5a**) and (**5a<=>2a**). During the forward isomerization of model imines (**2a<=>5a**) electron-donating substituents (*p*-OMe) cause an increase in the reaction rate. This can not be explained when the

deprotonation of imine **2a** is the rate determinating step in the isomerization process. The first step in the isomerization is the deprotonation of the imine **2a** and for deprotonation to occur the $\Delta G^{\#}_A$-value of 68.5 kJ/mol has to be overcome (Figure 5.14).

In comparison with model imine **1b** the difference in $\Delta G^{\#}_A$-values is ca. 13.5 kJ/mol and deprotonation of the imine **2a** as compared to **1b** is facilitated. For model imine **3a** the difference in $\Delta G^{\#}_A$-values is ca. 13.7 kJ/mol, which is comparable with the energy difference for **1b** and **2a**. The reason for the different behavior of imines **2a** and **3a** can be explained by taking into account the relative aza-allyl anion stabilities **2a'** and **3a'** (Figures 5.7, 5.14 and 5.15). Since the aza-allyl anion-base complexes **2a'** and **3a'** are stabilized by two and three phenyl groups, respectively, as compared to only one phenyl group for imine **1b**, a better conjugation will be present in the anion complexes **2a'** and **3a'**. The relative energy levels of the intermediate aza-allyl anions **1b'**, **2a'** and **3a'** can not be determined with the Eyring, Arrhenius, and Gibbs methodology. The difference in the values of $\Delta G^{\#}$ for imines **1b**, **2a** and **3a** in combination with the difference in stability of the intermediate aza-allyl anions **1b'**, **2a'** and **3a'** are responsible for the reversal of the *p*-substituent behavior of imines **1b** with **2a** and **3a**.

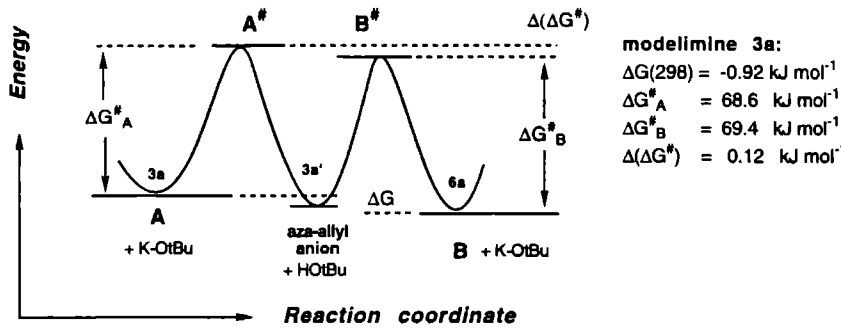


Figure 5.15

The equilibrium constants for the isomerization reaction of the *para*-substituted model imines **1a-e**, **2a-e** and **3a-e** at different temperatures are shown in Table 5.10 and the Hammett plots for the equilibrium constants at T=25°C are depicted in Figure 5.16.

Table 5.10 Equilibrium constants for the isomerization reaction of *para*-substituted model imines **1a-e**, **2a-e** and **3a-e** at different temperatures

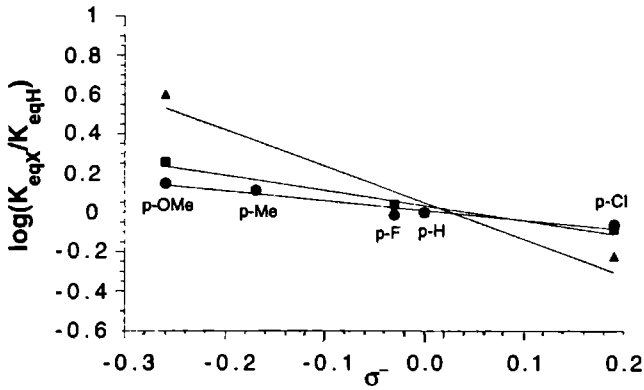
	Model imines **1a-e**	Model imines **2a-e**		Model imines **3a-e**	
X=	K_{eq}[a] (T=22°C)	K_{eq}[a] (T=-18°C)	K_{eq}[b] (T=25°C)	K_{eq}[a] (T=-40°C)	K_{eq}[b] (T=25°C)
H	9.48	2.93	2.27	2.10	1.45
Cl	8.19	1.53	1.36	1.60	1.19
OMe	13.3	13.2	9.05	4.46	2.61
Me	12.2	--	--	--	--
F	9.17	2.74	2.26	2.38	1.59

a) Experimental K_{eq} values. b) K_{eq} values determined by extrapolation of the Gibbs-plots.

The best linear Hammett relationships were obtained, when σ^- substituent constants were used. The plots show that the Hammett constants ρ for model imines **1a-e**, **2a-e** and **3a-e** are negative in all cases and have values of -0.50, -1.85 and -0.77, respectively. The correlation coefficients (R) are higher than 0.95. The best linear Hammett relationships were obtained, when

σ^- substituent constants were used. The plots show that the Hammett constants ρ for model imines **1a-e**, **2a-e** and **3a-e** are negative in all cases and have values of -0.50, -1.85 and -0.77, respectively. The correlation coefficients (R) are higher than 0.95.

Figure 5.16 Hammett plots of the equilibrium constants for the isomerization of model imines **1a-e**, **2a-e** and **3a-e**.

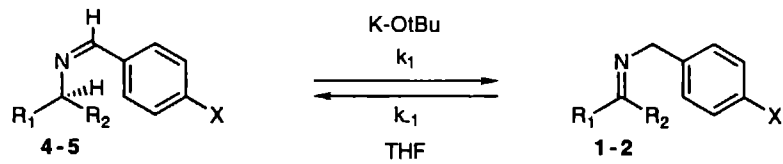


● = $\ln(K_{eqX}/K_{eqH})$-imine (**1a-e**); ▲ = $\ln(K_{eqX}/K_{eqH})$-imine (**2a-e**); ■ = $\ln(K_{eqX}/K_{eqH})$-imine (**3a-e**).

For model imines **2a-e** and **3a-e** a larger substituent effect on the equilibrium values of the isomerization reaction is found. This behavior may be explained by the higher conjugation present in the aza-allyl anion intermediates derived from **2a-e** and **3a-e**. This high conjugation in the aza-allyl anions derived from **2a-e** and **3a-e** is responsible for the increased influence of the substituents on the equilibrium value of the isomerization reaction.

5.2.6 Racemization experiments

The reaction conditions used for the isomerization of imines **1b**, **2a** and **3a** into their corresponding product imines **4b**, **5a** and **6a** were also applied to investigate the reverse imine isomerization reaction starting from chiral imines **4b** and **5b**. During these experiments the reaction constants (k_1 and k_{-1}) as well as the racemization constant (k_{rac}) of the starting imines **4b** and **5b** (X=Cl) were obtained using GLC and HPLC techniques. The reaction is depicted in Scheme 5.3.



4,1: $R_1 = PhCH_2CH_2$, $R_2 = CH_3$
5,2: $R_1 = Ph$, $R_2 = CH_3$

X = Cl (**b**)

Scheme 5.3

The kinetic results of the isomerization reactions of model imines **4b** and **5b** are shown in Table 5.11 and are compared with the isomerization results determined for the conversion of **1b** to

4b and **2b** to **5b**. The determination of k_{rac} was performed using linear plots of ln[e.e(%)] versus time as derived in the appendix (equation A.27) and is shown in Figure 5.17.

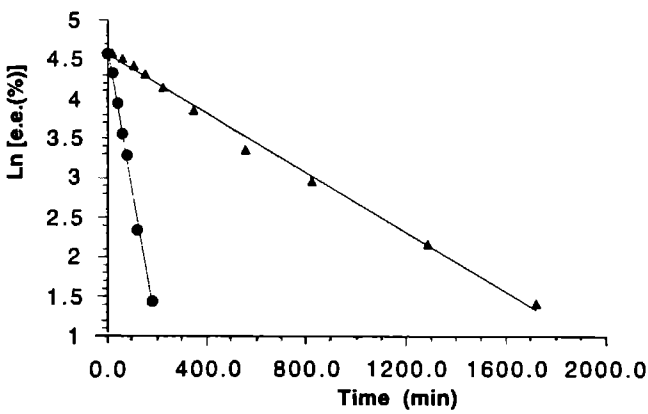
Table 5.11 Isomerization and racemization kinetics of model imines **4b** and **5b**.

Entry (imine)	Temp. °C (K)	K_{eq} ($1/K_{eq}$)	k_{rac} (10^{-3} min^{-1})	k_1 (10^{-3} min^{-1})	k_{-1} (10^{-3} min^{-1})	k_{exp} (10^{-3} min^{-1})
1 (**4b**)	22 (295)	0.121 (8.30)	0.95	2.98	24.7	27.7
2 (**1b**)	22 (295)	8.19	--	23.1	2.82	25.9
3 (**5b**)	-18 (255)	0.63 (1.60)	9.0	32.2	51.4	83.6
4 (**2b**)	-18 (255)	1.53	--	42.2	27.6	69.8

a) [imine **4b**,**1b**] = 0.1 mmol/mL. b) [base] = 0.6 equivalent (0.06 mmol/mL). c) [imine **5b**,**2b**] = 0.05 mmol/mL. d) [base] = 0.3 equivalent (0.015 mmol/mL).c) $k_{exp} = k_1 + k_{-1}$ (see appendix).

During the imine isomerization and racemization processes, the reaction conditions were identical to those used for the temperature dependent analysis and the Hammett analysis. The results in Table 5.11 reveal that in both the forward (**1b=>4b** and **2b=>5b**) and reverse (**4b=>1b** and **5b=>2b**) imine isomerization experiments the equilibrium constants (K_{eq}) and the reaction constants (k_1 and k_{-1}) reach almost similar values. The reaction constant (k_1, entry 2) for the reaction **1b=>4b** has to be compared with the value of the reaction constant (k_{-1}, entry 1) of the reaction **4b=>1b** and vice versa. For the isomerization of the imine systems **1b<=>4b** and **2b<=>5b** the experimental errors are 3.5 % and 8.5 %, respectively. The inaccuracies are within the range of the average experimental errors found in the imine isomerization experiments in section 5.2.4 (errors ca. 5 and 10%, respectively).

Figure 5.17 Plot of racemization for the model imines **4b** and **5b**.

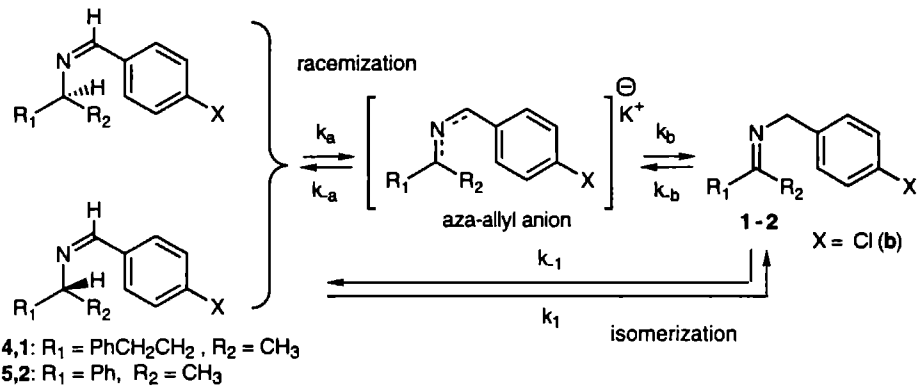


▲ = ln(e.e(%))-imine (**4b**); ● = ln(e.e(%))-imine (**5b**);

For model imines **4b** and **5b** the racemization constants (k_{rac}) were determined to be $0.95*10^{-3}$ min^{-1} and $9.0*10^{-3}$ min^{-1}, respectively. Comparison of these racemization constants (k_{rac}) with the reaction constant (k_1) for **4b=>1b** (entry 1) and **5b=>2b** (entry 3) reveals that for both imines **4b** and **5b** the racemization reaction constant is smaller than the values of k_1 (entries 1

and 3). The values of k_1/k_{rac} were calculated for imine **4b** and **5b** and were found to be 3.1 and 3.6, respectively.

The isomerization and the racemization processes are shown in Scheme 5.4. The racemization rate constant is expected to be higher than the isomerization rate constant, because the racemization reaction can occur via two pathways. First, a direct racemization after deprotonation followed by a direct protonation of the intermediate aza-allyl anion yielding the antipodes of the starting imines **4b** and **5b** can be envisioned.



Scheme 5.4

A second route toward racemized products **4b** and **5b** may occur via the isomerization of **4b** and **5b** into **1b** and **2b** and vice versa. The reason that a lower racemization rate is found may be the presence of intimate ion-pairs[18] consisting of an aza-allyl anion, a potassium ion (K^+), a tertiary butyl alcohol molecule and one or more additional chiral imines **4b** and **5b**. During the isomerization and the racemization of the aza-allyl anion, intermolecular chirality transfer induced by the excess chiral imines **4b** and **5b** present in the aforementioned complex may occur. The enantioselectivity in the proton transfer for the isomerization of imines **4b** and **5b** was calculated from the the relation between (k_1/k_{rac}) and amount to 31% and 36%, respectively.

The observed behavior in the isomerization and racemization of chiral imines is of interest in connection with the proposed catalytic asymmetric imine isomerization reaction (chapter 6). From the aforementioned results it can be concluded that if an asymmetric imine isomerization catalyzed by chiral catalysts is possible, enantiomerically enriched imines, although being racemized during the isomerization process, may be isolated during the reaction. This racemization process, which is an intrinsic phenomena in the isomerization equilibrium reactions of imines, has a lower rate than the isomerization. Therefore, imines and their corresponding amines resulting from asymmetrically catalyzed isomerization reactions may be isolated before extensive racemization has occurred. Another important result from the racemization experiments is that additional evidence for the presence of an aza-allyl anion intermediate in the imine isomerization process is obtained and that the concerted mechanism can be excluded.

5.3 Concluding remarks

Evidence for the occurrence of aza-allyl anions as essential intermediates in the imine isomerization reaction was obtained using Eyring, Arrhenius, and Gibbs energy data in combination with Hammett analysis and racemization experiments of model imines **1a-e**, **2a-e**, **3a-e**, **4b** and **5b**.

The best correlation in the Hammett plots of model imines **1a-e**, **2a-e** and **3a-e** was obtained when σ^- substituent constants were used, which is an indication for the presence of

negatively charged reaction intermediates in the imine isomerization reaction. Evidence for the presence of aza-allyl anions during the isomerization process was also obtained from the relatively high values of the Hammett reaction constants ($1.70<|\rho|<3.8$). For imines **1a-e** and **2a-e** and **3a-e** a different influence of *p*-substituents was observed. From the Hammett plots for model imines **1a-e**, derived from benzylacetone and *p*-X benzylamines, **2a-e**, those from acetophenone and *p*-X benzylamines, and **3a-e**, those from benzophenone and *p*-X benzylamines, a difference in behavior of the three *p*-substituted model imines was observed. The model imines **1a-e** show an increase in the isomerization rate in the presence of electron-withdrawing groups (*p*-Cl). However, for model imines **2a-e** and **3a-e** the presence of electron-donating substituents (*p*-OMe) results in an increase in the imine isomerization reaction rate. This difference was explained by a difference in the rate determinating step during the isomerization reaction. For imines **1a-e** the deprotonation was the rate determining reaction step in the isomerization process, whereas for imines **2a-e** and imines **3a-e**, the protonation of the intermediate aza-allyl anion is expected to be rate determining.

The relative reaction rates of the isomerization of model imines **1a-e**, **2a-e** and **3a-e** were determined as **1b** : **2a** : **3a** = 1 : 850 : 915 at room temperature. The difference in reaction rates of the isomerization could be explained using the Eyring analysis of **1b**, **2a** and **3a** in combination with the stability of the intermediate aza-allyl anions **1b'**, **2a'**, and **3a'** (Figure 5.7). The overall free energy of activation ($\Delta G^{\#}$) for isomerization reaction (k_{obs}) for imines **1a**, **2a** and **3a** amounted to 81.6, 67.6 and 67.3 kJ/mol, respectively.

Additional evidence for the presence of aza-allyl anions in the isomerization process was obtained from the racemization experiments with model imines **4b** and **5b**. The rate of racemization is lower than the rate of isomerization, which can not be explained with a concerted reaction mechanism and therefore aza-allyl anions must play an important role in the imine isomerization reaction. This relatively low racemization reaction rate as compared to the isomerization rate is indicative of an intermolecular chirality transfer during the isomerization process. An intermolecular chirality transfer in the isomerization of imines was also observed by Cram and coworkers, and is an interesting property in view of the asymmetric catalytic imine isomerization.

5.4 Experimental section

General Methods. All reactions were conducted under an atmosphere of argon, using standard Schlenk techniques. Optical rotations were determined with a Perkin-Elmer automatic polarimeter, model 241 MC, using 1% solutions at 20°C in the solvents indicated. Melting points were determined using a Reichert thermopan microscope equipped with crossed polarizers, and are uncorrected. GLC was conducted with a Hewlett-Packard HP5890A and HP 5790A gas chromatograph, using a capillary column (25m) of HP-1 and PAS-1701, a temperature program from 190-250°C at 10°C/min, followed by 10 min at 250°C (isothermal), and nitrogen at 2 ml/min (0.5 atm) as the carrier gas. The instruments were connected to a HP 3396 or HP 3390 calculating integrator The enantiomeric purity of imines **4** and **5** was determined by HPLC[19] using a chiral column with n-hexane/2-propanol (ratio as indicated) as the eluent. The chromatographic system consisted of a Pharmacia LKB (Sweden) model 2150 HPLC pump, a LKB model 2152 HPLC controller and a Rheodyne injector. The injection loop had a 20-µl capacity. The column used was a Daicel Chiralpak AD (250*4.6 mm I.D., 10 µm) from J.T. Baker (Deventer, The Netherlands). The flow rate was 0.60 ml/min or 0.75 ml/min and the column was operated at ambient temperature. The column effluent was monitored with a LKB model 2138 uvicord S absorbance detector at 254 nm UV spectra of Schiff base derivatives were recorded with a Perkin-Elmer lamba 5 UV/Vis spectrofotometer ^{1}H- and ^{13}C-NMR were performed on a Bruker AC 100 (100 MHz, FT) or a Bruker AM-400 (400 MHz, FT) spectrometer using solutions in $CDCl_3$ (internal Me_4Si). IR spectra were determined on a Perkin Elmer 298 spectrophotometer. FT IR spectra were determined on a Biorad WIN-IR FTS-25 spectrophotometer. Elemental analyses were performed on a Carlo Erba Instruments CHNS-O EA 1108 element analyzer. Electron impact (EI) and chemical ionization (CI) mass spectra, induced with methane gas at 200°C and emission current 0.5 mA, were determined on a VG 7070E spectrometer. For GC-MS spectroscopy, a Varian Saturn benchtop GC-MS apparatus with a Varian 8100 autosampler was used. MS analysis was performed using electron impact (EI).

Chemicals Diethyl ether was pre-dried over calcium chloride, then distilled from calcium hydride Tetrahydrofuran was distilled from potassium/benzophenone under Schlenk conditions and stored under argon Benzene and absolute ethanol (both Merck p a quality) were used without further purification All other solvents were either P A or "reinst' quality (±)- and (R)-(+)-4-phenyl-2-aminobutane were obtained from DSM-Andeno (Venlo, the Netherlands) K-OtBu was sublimed (0 1 mm Hg, T=180°C) and stored under argon All other reagents are commercially available and were used as received Unless otherwise stated, yields refer to isolated yields of products of greater than 95% purity as estimated by capillary GC and / or ^{1}H NMR spectroscopy

Procedure A for the preparation of imines derived from 4-phenyl-2-butanone (1a-e).
4-Phenyl-2-butanone (1 equiv) and the appropriate *p*-substituted amine (1 equiv) were mixed using solvent free reaction conditions Vacuum dried $MgSO_4$ was gradually added until the reaction mixture became solid After 12 h the solid mixture was dissolved in dry diethyl ether and the remaining $MgSO_4$ was removed by filtration, followed by the removal of the solvent *in vacuo* The reaction was monitored using GLC In most cases this procedure was repeated several times and additions of fresh $MgSO_4$ were necessary to complete the reaction The imines were isolated in high purities (>97%) and used as such in the imine isomerization experiments The ratio of geometric isomers was determined by ^{1}H NMR spectroscopy

Procedure B for the preparation of imines derived from 4-phenyl-2-butanone (1a-e).
4-Phenyl-2-butanone (1 equiv) and the appropriate *p*-substituted amine (1 equiv) were mixed using solvent free reaction conditions Vacuum dried molecular sieves (3Å) were added and after 12 h the molecular sieves were removed and replaced by fresh ones In most cases this procedure was repeated for 3 or 4 times to complete the reaction The reaction was monitored by GLC The imines were isolated in high purities (>97%) and used as such in the imine isomerization experiments The ratio of geometric isomers was determined by ^{1}H NMR spectroscopy

Procedure C for the preparation of imines derived from acetophenone (2a-e) and benzophenone (3a-e).
The ketone (1 equiv) and the appropriate *p*-substituted amine (1 equiv) were dissolved in dry benzene (50-250 mL) under argon The reaction flask was equipped with a reflux condenser combined with a Dean Stark trap and after the addition of borontrifluoride-etherate (BF_3-OEt_2, 48%) (0 02 equiv) the mixture was heated under reflux for 3-24 h When the reaction was complete the solvent was removed *in vacuo* Diethyl ether was added to the crude reaction product followed by the extraction with saturated aqueous $NaHCO_3$ The combined organic layers were dried over $MgSO_4$, filtered over silicagel and concentrated *in vacuo* The reaction was monitored by GLC The imines were purified by recrystallization from EtOH The ratio of geometric isomers was determined by ^{1}H NMR spectroscopy

Procedure D for the preparation of imines 4a-e and 5b,d.
The chiral amine (1 equiv) and the appropriate *p*-substituted aldehyde (1 equiv) were dissolved in dry diethyl ether (25-100 mL) under argon Vacuum dried $MgSO_4$ was gradually added and after 24 h the $MgSO_4$ was removed by filtration over a glass filter, followed by the addition of fresh $MgSO_4$ The reaction was monitored using GLC In most cases the addition of a small amount of aldehyde or chiral amine was necessary to complete the reaction This procedure was continued until a purity of 99 5% was reached, and followed by the removal of $MgSO_4$ by filtration and the solvent *in vacuo* The imines were isolated in high purities (>99%) and used as such in the imine isomerization experiments The enantiomeric purity of imines **4a-e** and **5a-e** was determined before hydrolysis using HPLC[20] and after hydrolysis using GLC (Mosher acid chloride and/or camphanoyl derivative[21]) and HPLC (*p*-Cl-aldehyde imine derivative) of the corresponding amines Detailed information on the use of HPLC in the separation of imine enantiomers is described in chapter 7

***N*-(1-Methyl-3-phenyl-propylidene)benzylamine (1a, R_1 = $PhCH_2CH_2$, R_2 = CH_3, X=H).**
Procedure B was followed using benzylamine (11 7 g, 107 mmol) and 4-phenyl-2-butanone (15 7 g, 106 mmol) The reaction was completed in 5 days affording 23 9 g (95%) of product with a purity of 96 5% (GLC) as a 1 5 mixture of syn/anti isomers HRMS Calc for $C_{17}H_{19}N$ 237 1517 found 237 1516 MS (EI) m/e 237 (M^+, 50%), 146 (M^+-$PhCH_2$, 35%), 91 ($PhCH_2^+$, 100%), 105 ($PhCH_2CH_2^+$,14%), 77 (Ph^+, 6%) ^{1}H NMR (100 MHz in $CDCl_3$) δ 7 30-7 10 (d, 10H, ArH), 4 45 (s, 2H, CH_2 benzyl, anti-confm), 4 36 (s, 2H, CH_2 benzyl, syn-confm), 2 99-2 78 (m, 2H, $PhCH_2$), 2 68 (m, 2H $PhCH_2CH_2$), 2 0 (s, 3H, CH_3, syn-confm), 1 83 (s, 3H, CH_3, anti-confm) ppm ^{13}C NMR (25 2 MHz, $CDCl_3$) δ 170 0 (C=N), 141 8-125 8 (aromatic C), 55 0 (CH_2 benzyl), 44 0 ($PhCH_2CH_2$), 32 6 ($PhCH_2CH_2$), 18 1 (CH_3) ppm IR (CCl_4) ν=1644 (C=N) cm^{-1}

***N*-(1-Methyl-3-phenyl-propylidene)-4-chlorobenzylamine (1b, R_1 = $PhCH_2CH_2$, R_2 = CH_3, X=Cl).**

Procedure A was followed using 4-chlorobenzylamine (16 3 g, 0 115 mol) and 4-phenyl-2-butanone (14 8 g, 0 100 mol) Purification by recrystallization from ethanol (3x) gave 12 10 g (44 5 %) of product **1b** as a 1 4 mixture of syn/anti isomers, m p 52 8 °C Calc for $C_{17}H_{18}NCl$ (271 79) C 75 13, H 6 68, N 5 15 %, found C 74 93, H 6 73, N 5 11 % MS(CI) m/e 272 ($M+1^+$, 60%), 180 ($M+1^+$-$PhCH_2$, 47%), 125 (4-Cl-$PhCH_2^+$, 100%), 105 ($PhCH_2CH_2^+$,17%), 91 ($PhCH_2^+$, 18%), 77 (Ph^+, 6%) ^1H NMR (100MHz, $CDCl_3$) δ 7 26-7 20 (m, 9H, ArH), 4 43 (s, 2H, CH_2 benzyl, anti-confm), 4 32 (s, 2H, CH_2 benzyl, syn-confm), 2 94-2 67 (m, 4H, $PhCH_2CH_2$), 2 14 (t, 3H, CH_3, syn-confm , J=0 2 Hz), 1 90 (s, 3H, CH_3, anti-confm) ppm ^{13}C NMR (25 2 MHz, $CDCl_3$) δ 170 4 (C=N), 141 7-125 9 (aromatic C), 54 3 (CH_2 benzyl), 44 0 ($PhCH_2CH_2$), 32 5 ($PhCH_2CH_2$), 18 2 (CH_3) ppm IR (KBr) ν = 1664 (C=N) cm^{-1}

***N*-(1-Methyl-3-phenyl-propylidene)-4-methoxybenzylamine (1c, R_1 = $PhCH_2CH_2$, R_2 = CH_3, X=OMe).**

Procedure A was followed using 4-methoxybenzylamine (10 5 g, 77 mmol) and 4-phenyl-2-butanone (11 3 g, 77 mmol) The reaction was completed in 5 days affording 19 6 g (95%) of the product with a purity of 96 7% (GLC) as a 1 4 5 mixture of syn/anti isomers HRMS Calc for $C_{18}H_{21}NO$ 267 1623 found 267 1622 MS (EI) m/e 267 (M^+, 11%), 176 (M^+-$PhCH_2$, 11%), 121 (4-MeO-$PhCH_2^+$, 100%), 91 ($PhCH_2^+$, 41%), 77 (Ph^+, 16%) ^1H NMR (100MHz in $CDCl_3$) δ 7 2-6 8 (m 9H, ArH), 4 4 (s, 2H, CH_2 benzyl, anti-confm), 4 3 (s, 2H, CH_2 benzyl, syn-confm), 3 8 (s, 3H, OCH_3), 3 0-2 8 (m, 2H, $PhCH_2CH_2$), 2 7-2 5 (m, 2H, $PhCH_2CH_2$), 2 1 (s, 3H, CH_3, syn-confm), 1 9 (s, 3H, CH_3, anti-confm) ^{13}C NMR (25 2 MHz in $CDCl_3$) δ 169 7 (C=N), 158 3 113 8 (aromatic C), 55 3 (OCH_3), 54 5 (CH_2 benzyl, anti-confm), 54 2 (CH_2 benzyl, syn-confm), 44 1 ($PhCH_2CH_2$), 32 7 ($PhCH_2CH_2$), 18 0 (CH_3) ppm IR (CCl_4) ν = 1663 (C=N) cm^{-1}

***N*-(1-Methyl-3-phenyl-propylidene)-4-methylbenzylamine (1d, R_1 = $PhCH_2CH_2$, R_2 = CH_3, X=CH_3).**

Procedure A was followed using 4-methylbenzylamine (9 52 g, 79 mmol) and 4-phenyl-2-butanone (11 1 g, 75 mmol) The reaction was completed in 5 days affording 17 9 g (95%) of the product with a purity of 96 5% (GLC) as a 1 4 5 mixture of syn/anti isomers ^1H NMR (100 MHz in $CDCl_3$) δ 7 21-7 12 (m, 9H, ArH), 4 43 (s, 2H, CH_2 benzyl, anti-confm), 4 36 (s, 2H, CH_2 benzyl, syn-confm), 2 84-2 44 (m, 4H $PhCH_2CH_2$), 2 05 (s, 3H, CH_3, syn-confm), 1 85 (s, 3H, CH_3, anti-confm), 0 95 (s, 3H, $PhCH_3$) ppm ^{13}C NMR (25 2 MHz, $CDCl_3$) δ 169 6 (C=N), 155 9-125 4 (aromatic C), 56 1 (CH_2 benzyl, syn conf), 54 8 (CH_2 benzyl anti conf), 44 0 ($PhCH_2CH_2$), 32 4 ($PhCH_2CH_2$), 21 1 ($PhCH_3$), 18 0 (CH_3) ppm IR (CCl_4) ν = 1663 (C=N) cm^{-1}

***N*-(1-Methyl-3-phenyl-propylidene)-4-fluorobenzylamine (1e, R_1 = $PhCH_2CH_2$, R_2 = CH_3, X=F).**

Procedure B was followed using 4-fluorobenzylamine (5 03 g, 40 2 mmol) and 4-phenyl-2-butanone (5 89 g, 39 8 mmol) The reaction was completed in a week affording 9 65 g (95%) of the product with a purity of 98 5% (GLC) as a 1 3 7 mixture of syn/anti isomers HRMS Calc for $C_{17}H_{18}NF$ 255 1423 found 255 1424 MS (EI) m/e 255 (M^+, 16%), 164 (M^+-$PhCH_2$, 29%), 109 (4-F-$PhCH_2^+$, 100%), 91 ($PhCH_2^+$, 65%), 77 (Ph^+, 9%) ^1H NMR (100 MHz in $CDCl_3$) δ 7 22-6 87 (m, 9H, ArH), 4 41 (s, 2H, CH_2 benzyl, anti-confm), 4 31 (s, 2H, CH_2 benzyl, syn-confm), 3 02-2 85 (m, 2H, $PhCH_2CH_2$), 2 71-2 55 (m, 2H, $PhCH_2CH_2$), 2 08 (s, 3H, CH_3, syn-confm), 1 88 (s, 3H, CH_3, anti-confm) ppm ^{13}C NMR (25 2 MHz, $CDCl_3$) δ 170 2 (C=N), 166 5 114 6 (aromatic C), 54 3 (CH_2 benzyl, anti-confm), 53 9 (CH_2 benzyl, syn-confm), 44 0 ($PhCH_2CH_2$), 32 5 ($PhCH_2CH_2$), 18 1 (CH_3) ppm IR (CCl_4) ν = 1663 (C=N) cm^{-1}

***N*-(1-Methylbenzylidene)benzylamine (2a, R_1 = Ph, R_2 = CH_3, X=H).**[22]

Procedure C was followed using benzylamine (11 25 g, 105 mmol) and acetophenone (12 0 g, 100 mmol) Purification by recrystallization from ethanol (3x) afforded 9 2 g (45%) of the product with a purity of 99 5% (GLC) as a 1 12 mixture of syn/anti isomers, m p 42-44 5 °C Calc for $C_{15}H_{15}N$ (209 7) C 86 08, H 7 22, N 6 69 %, found C 85 96, H 7 17, N 6 73 % MS (EI) m/e 209 (M^+, 35%), 91 ($PhCH_2^+$, 100%), 77 (Ph^+, 11%) ^1H-NMR (100 MHz in $CDCl_3$) δ 7 89-7 75 (m, 2H, aromatic), 7 44-7 08 (m, 8H, aromatic), 4 66 (s, 2H, CH_2 benzyl, anti conf), 4 41 (s, 2H, CH_2 benzyl, syn conf), 2 25 (s, 3H, CH_3) ppm ^{13}C-NMR (25 2 MHz in $CDCl_3$) δ 165 9 (C=N), 141 2-126 0 (aromatic C), 57 4 (benzyl CH_2, syn conf), 55 6 (benzyl CH_2, anti conf), 15 93 (CH_3) ppm IR (CCl_4) υ = 3100-3000 (aromatic), 2940-2850 (alkyl), 1630 (C=N) cm^{-1}

***N*-(1-Methylbenzylidene)-4-chlorobenzylamine (2b, R_1 = Ph, R_2 = CH_3, X=Cl).**

Procedure C was followed using 4-chlorobenzylamine (11 4 g, 100 mmol) and acetophenone (14 2 g, 100 mmol) Purification by recrystallization from ethanol (3x) gave 9 8 g (40%) of the product with a purity of 99 5% (GLC) as a 1 14 mixture of syn/anti isomers, m p 47-49 °C Calc for $C_{15}H_{14}NCl$ (243 8) C 73 92, H 5 75, N 5 79 %, found C 73 88, H 5 85, N 5 73 % MS (EI) m/e 243 (M^+, 31%), 125 (p-Cl-$C_6H_4CH_2^+$, 100%), 77 (Ph^+, 12%) ^{1}H-NMR (100 MHz in $CDCl_3$) δ 7 90-7 76 (m, 2H, aromatic), 7 41-7 11 (m, 7H, aromatic), 4 66 (s, 1H, CH_2 benzyl, anti conf), 4 37 (s, 1H, CH_2 benzyl, syn conf), 2 32 (s, 3H, CH_3) ppm ^{13}C (25 2 MHz in $CDCl_3$) δ 166 2 (C=N), 140 7-125 6 (aromatic C), 56 4 (benzyl CH_2, syn conf), 54 9 (benzyl CH_2, anti conf), 15 7 (CH_3) ppm IR (CCl_4) υ = 3080-3000 (aromatic), 2940-2870 (alkyl), 1630 (C=N) cm^{-1}

***N*-(1-Methylbenzylidene)-4-methoxybenzylamine (2c, R_1 = Ph, R_2 = CH_3, X=OMe).**
Procedure C was followed using 4-methoxybenzylamine (4 53 g, 33 mmol) and acetophenone (3 96 g, 33 mmol) Purification by recrystallization from ethanol (2x) gave 3 36 g (42%) of the product with a purity of 99 8% (GLC) as a 1 13 mixture of syn/anti isomers, m p 53-55°C Calc for $C_{16}H_{17}NO$ (239 7) C 80 30, H 7 16, N 5 85%, found C 80 23, H 7 20, N 5 90% MS (EI) m/e 239 (M^+, 15%), 121 (p-MeO-$C_6H_4CH_2^+$, 100%), 91 ($PhCH_2^+$, 25%), 77 (Ph^+, 23%) ^{1}H-NMR (100 MHz in $CDCl_3$) δ 7 93-6 80 (m, 9H, aromatic), 4 67 (s, 2H, benzyl CH_2, anti conf), 4 36 (s, 2H, benzyl CH_2, syn conf), 3 74 (s, 3H,O$\underline{C}H_3$), 2 29 (s, 3H, CH_3) ppm ^{13}C (25 2 MHz in $CDCl_3$) δ 165 4 (C=N), 158-113 6 (aromatic C), 56 6 (benzyl CH_2, syn conf), 55 1 (benzyl CH_2, anti conf), 54 9 (O$\underline{C}H_3$), 15 6 (CH_3) ppm IR (CCl_4) 3100-3000 (aromatic), 2980 2880 (alkyl), 1635 (C=N) cm^{-1}

***N*-(1-Methylbenzylidene)-4-fluorobenzylamine (2e, R_1 = Ph, R_2 = CH_3, X=F).**
Procedure C was followed using 4-fluorobenzylamine (6 25 g, 50 mmol) and acetophenone (6 00 g, 50 mmol) Purification by recrystallization from ethanol (2x) afforded 6 3 g (55%) of the product with a purity of 99 8% (GLC) as a 1 13 mixture of syn/anti isomers, m p 35-36 °C Calc for $C_{15}H_{14}NF$ (227 3) C 79 27, H 6 21, N 6 16 %, found C 79 09, H 6 13, N 6 22 % MS (EI) m/e 227 (M^+, 32%), 149 (M^+-C_6H_5, 18%), 109 (p-F-$PhCH_2^+$ 100%) ^{1}H-NMR (100 MHz in $CDCl_3$) δ 7 89-7 79 (m, 2H, aromatic), 7 45-7 31 (m, 5H, aromatic), 7 19-6 92 (m, 2H, aromatic), 4 65 (s, 2H, benzyl CH_2, anti conf), 4 37 (s, 2H, benzyl CH_2, syn conf), 2 29 (s, 3H, CH_3) ppm ^{13}C (25 2 MHz in $CDCl_3$) δ 166 7 (C=N), 166 2-114 7 (aromatic C), 56 6 (benzyl CH_2, syn conf), 55 0 (benzyl CH_2, anti conf), 16 0 (CH_3) ppm IR (CCl_4) υ= 3100-3000 (aromatic), 2970-2800 (alkyl), 1640 (C=N) cm^{-1}

***N*-(1-phenylbenzylidene)-benzylamine (3a, R_1 = Ph, R_2 = Ph, X=H).**
Procedure C was followed using benzylamine (9 27 g, 86 5 mmol) and benzophenone (15 0 g, 82 3 mmol) Purification by recrystallization from ethanol (3x) gave 15 7 g (70%) of the product with a purity of 99 8% according to capillary GLC, m p 57-60°C Calc for $C_{20}H_{17}N$ (271 36) C 88 52, H 6 31, N 5 16 %, found C 88 57 H 6 23, N 5 21 % MS (EI) m/e 271 (M^+, 100%), 165 (Ph_2C^+ 15%), 91 ($PhCH_2^+$, 22%) ^{1}H-NMR (100 MHz in $CDCl_3$) δ 7 75-7 65 (m, 2H, aromatic), 7 46-7 13 (m, 13H, aromatic), 4 61 (s, 2H, benzyl CH_2), ppm ^{13}C (25 2 MHz in $CDCl_3$) δ 168 7 (C=N), 140 6-126 5 (aromatic C), 57 4 (benzyl CH_2) ppm IR (KBr) υ= 3100-3000 (aromatic), 2970-2800 (alkyl), 1617 (C=N) cm^{-1}

***N*-(1-phenylbenzylidene)-4-chlorobenzylamine (3b, R_1 = Ph, R_2 = Ph, X=Cl).**
Procedure C was followed using 4-chlorobenzylamine (12 2 g, 86 5 mmol) and benzophenone (14 9 g, 82 3 mmol) Purification by recrystallization from ethanol (4x) gave 16 6 g (66%) of the product with a purity of 99 6% according to capillary GLC, m p 68-70°C Calc for $C_{20}H_{16}ClN$ (305 81) C 78 55, H 5 27, N 4 58 %, found C 78 67, H 5 21, N 4 59 % MS (EI) m/e 305 (M^+, 100%), 165 (Ph_2C^+ 40%), 125 (4-Cl-$PhCH_2^+$, 61%) ^{1}H-NMR (100 MHz in $CDCl_3$) δ 7 63-7 51 (m, 2H, aromatic), 7 46-6 95 (m, 13H, aromatic), 4 54 (s, 2H, benzyl CH_2), ppm ^{13}C (25 2 MHz in $CDCl_3$) δ 169 1 (C=N), 139 5-127 6 (aromatic C), 56 6 (benzyl CH_2) ppm IR (KBr) υ= 3100-3000 (aromatic), 2970-2800 (alkyl), 1623 (C=N) cm^{-1}

***N*-(1-phenylbenzylidene)-4-methoxybenzylamine (3c, R_1 = Ph, R_2 = Ph, X=OMe).**
Procedure C was followed using 4-methoxybenzylamine (3 6 g, 2 6 mmol) and benzophenone (4 3 g, 23 6 mmol) Purification by recrystallization from ethanol (2x) gave 5 9 g (83%) of the product with a purity of 99 9% according to capillary GLC, m p 66 67°C Calc for $C_{21}H_{19}NO$ (301 37) C 83 69, H 6 35, N 4 65 %, found C 83 82, H 6 28, N 4 78 % MS (EI) m/e 301 (M^+, 45%), 165 (Ph_2C^+ 10%), 121 (4-MeO-$PhCH_2^+$, 100%) ^{1}H-NMR (100 MHz in $CDCl_3$) δ 7 62-7 52 (m, 2H, aromatic), 7 40-7 00 (m, 10H, aromatic), 6 82-6 70 (m, 2H, aromatic), 4 54 (s, 2H, benzyl CH_2), 3 75 (s, 3H, O$\underline{C}H_3$), ppm ^{13}C (25 2 MHz in $CDCl_3$) δ 168 4 (C=N), 158 3-113 7

(aromatic C), 56 6 (benzyl CH_2), 55 2 (O$\underline{C}H_3$) ppm IR (KBr) υ= 3100-3000 (aromatic), 2970-2800 (alkyl), 1613 (C=N) cm^{-1}

***N*-(1-phenylbenzylidene)-4-methylbenzylamine (3d, R_1 = Ph, R_2 = Ph, X=CH_3).**
Procedure C was followed using 4-methylbenzylamine (3 20 g, 27 mmol) and benzophenone (4 50 g, 24 7 mmol) Purification by recrystallization at T = -69°C from ethanol (2x) afforded 2 2 g (31%) of the product with a purity of 99 2% according to capillary GLC, m p ±20°C HRMS Calc for $C_{21}H_{19}N$ 285 1517 found 285 1517 MS (EI) m/e 285 (M^+, 73%), 165 (Ph_2C^+, 19%), 105 (4-Me-PhCH_2^+, 100%) ^{1}H-NMR (100 MHz in $CDCl_3$) δ 7 73-7 09 (m, 14H, aromatic), 4 57 (s, 2H, benzyl CH_2), 2 32 (s, 3H, C$\underline{H}_3$), ppm ^{13}C (25 2 MHz in $CDCl_3$) δ 166 3 (C=N), 139 6-127 4 (aromatic C), 57 1 (benzyl CH_2), 20 9 (C$\underline{H}_3$) ppm IR (CCl_4) υ= 1620 (C=N) cm^{-1}

***N*-(1-phenylbenzylidene)-4-fluorobenzylamine (3e, R_1 = Ph, R_2 = Ph, X=F).**
Procedure C was followed using 4-fluorobenzylamine (3 1 g, 25 mmol) and benzophenone (4 1g, 22 mmol) Purification by recrystallization from ethanol (2x) gave 5 7 g (88%) of the product with a purity of 99 9% according to capillary GLC, m p 79-81°C Calc for $C_{20}H_{16}NF$ (289 35) C 83 02, H 5 57, N 4 84%, found C 83 12, H 5 49, N 4 76 % MS (EI) m/e 289 (M^+, 100%), 165 (Ph_2C^+ 10%), 109 (4-F-PhCH_2^+, 65%) ^{1}H-NMR (100 MHz in $CDCl_3$) δ 7 62-7 51 (m, 2H, aromatic), 7 41-6 80 (m, 12H, aromatic), 4 54 (s, 2H, benzyl CH_2) ppm ^{13}C (25 2 MHz in $CDCl_3$) δ 168 7 (C=N), 166 5-114 6 (aromatic C), 56 6 (benzyl CH_2) ppm IR (KBr) υ= 3100-3000 (aromatic), 2970-2800 (alkyl), 1623 (C=N) cm^{-1}

(R)-benzylidene-(1-methyl-3-phenyl-propyl)-amine (4a, R_1 = $PhCH_2CH_2$, R_2 = CH_3, X=H).
Procedure D was followed using (R)-4-phenyl-2-aminobutane (3 63 g, 24 4 mmol) (e e =98 2%) and benzaldehyde (2 57 g, 24 4 mmol) The reaction was completed in 7 days affording 5 62 g (97%) of the product with a purity of 99 7% (GLC) in 1 geometric isomer m p 33 5 °C $[\alpha]_D^{20}$ = -104 0° (c=1, $CHCl_3$) Calc for $C_{17}H_{19}N$ (237 35) C 86 03, H 8 07 N 5 90, found C 85 76, H 8 23 N 5 89 % MS (CI) m/e 238 ($M+1^+$, 43%), 133 ($M+1^+$ $PhCH_2CH_2$, 100%), 105 ($PhCH_2CH_2^+$, 17%), 91 ($PhCH_2^+$, 38%), 77 (Ph^+, 7%) ^{1}H-NMR (100 MHz, $CDCl_3$) δ 8 26 (s, 1H, N=C$\underline{H}$), 7 80-7 71 (m, 2H, Ar$\underline{H}$), 7 51-7 19 (m, 8H, Ar$\underline{H}$), 3 34 (m, 1H, N-C$\underline{H}$, J=6 4 Hz), 2 68-2 48 (m, 2H, PhC$\underline{H}_2$CH$_2$), 2 07-1 85 (m, 2H, PhCH$_2$C$\underline{H}_2$), 1 28 (d, 3H, C$\underline{H}_3$, J=6 4 Hz) ppm ^{13}C-NMR (25 2 MHz in $CDCl_3$) δ 159 3 (C=N), 142 2-128 0 (aromatic C), 65 9 (N-$\underline{C}$H), 39 2 (Ph$\underline{C}H_2CH_2$), 32 8 (PhCH$_2\underline{C}H_2$), 22 6 (CH_3) ppm IR (CCl_4) ν=1644 (C=N) cm^{-1}

(R)-(4-chloro-benzylidene)-(1-methyl-3-phenyl-propyl)-amine (4b, R_1 = $PhCH_2CH_2$, R_2 = CH_3, X=Cl).
Procedure D was followed using (R)-4-phenyl-2-aminobutane (3 64 g, 24 4 mmol) (e e =98 2%) and 4-chlorobenzaldehyde (3 37 g, 24 mmol) The reaction was completed in 7 days affording 6 39 g (98%) of the product with a purity of 99 7% (GLC) in 1 geometric isomer m p 33 0 °C $[\alpha]_D^{20}$ -106 3° (c=1, $CHCl_3$) Calc for $C_{17}H_{18}NCl$ (271 80) C 75 13, H 6 68, N 5 15, found C 74 90, H 6 78 N 5 10 % MS (CI) m/e 272 ($M+1^+$, 42%), 167 ($M+1^+$-$PhCH_2CH_2^+$, 100%), 91 ($PhCH_2^+$, 37%), 77 (Ph^+, 5%) ^{1}H-NMR (100 MHz in $CDCl_3$) δ 8 23 (s, 1H, N=C$\underline{H}$), 7 78-7 26 (m, 9H, Ar$\underline{H}$), 3 38 (m, 1H, N-C$\underline{H}$, J=6 3 Hz), 2 74-2 55 (m, 2H, Ph$\underline{C}H_2CH_2$), 2 13-1 96 (m, 2H, PhCH$_2\underline{C}H_2$), 1 34 (d, 3H, C$\underline{H}_3$, J=6 3 Hz) ppm ^{13}C-NMR (25 2 MHz in $CDCl_3$) δ 157 7 (C=N), 142 2-125 8 (aromatic C), 65 9 (N-$\underline{C}$H), 39 3 (Ph$\underline{C}H_2$), 32 9 (PhCH$_2\underline{C}H_2$), 22 7 (CH_3) ppm IR (CCl_4) ν=1644 (C=N) cm^{-1}

(R)-4-methoxybenzylidene-(1-methyl-3-phenyl-propyl)-amine (4c, R_1 = $PhCH_2CH_2$, R_2 = CH_3, X=OMe).
Procedure D was followed using (R)-4-phenyl-2-aminobutane (0 91 g, 6 1 mmol) (e e =98 2%) and 4-methoxybenzaldehyde (0 83 g, 6 1 mmol) The reaction was completed in 7 days affording 1 55 g (95%) of the product with a purity of 96 8% (GLC) in 1 geometric isomer $[\alpha]_D^{20}$ = -115 6° (c=1, $CHCl_3$) HRMS Calc for $C_{18}H_{21}NO$ 267 1623, found 267 1622 MS (EI) m/e 267 (M^+, 15%), 162 (M^+-$PhCH_2CH_2$, 100%), 135 (MeO-$C_6H_4CH_2N^+$, 47%), 105 ($PhCH_2CH_2^+$, 20%), 91 ($PhCH_2^+$, 88%), 77 (Ph^+, 30%) ^{1}H-NMR (100 MHz in $CDCl_3$) δ 8 16 (s, 1H, N=C$\underline{H}$), 7 77-6 88 (m, 9H, Ar$\underline{H}$), 3 82 (s, 3H, OCH_3), 3 29 (m, 1H, N-C$\underline{H}$, J=6 3 Hz), 2 68-2 52 (m, 2H, PhC$\underline{H}_2$CH$_2$), 2 05-1 83 (m, 2H, PhCH$_2$C$\underline{H}_2$), 1 27 (d, 3H, C$\underline{H}_3$, J=6 3 Hz) ppm ^{13}C-NMR (25 2 MHz in $CDCl_3$) δ 161 7 (C=N), 158 8-114 1 (aromatic C), 65 9 (N-$\underline{C}$H), 55 5 (O$\underline{C}H_3$), 39 5 (Ph$\underline{C}H_2CH_2$), 33 1 (PhCH$_2\underline{C}H_2$), 22 9 (CH_3) ppm IR (CCl_4) ν=1641 (C=N) cm^{-1}

(R)-4-methylbenzylidene-(1-methyl-3-phenyl-propyl)-amine (4d, R_1 = $PhCH_2CH_2$, R_2 = CH_3, X=CH_3)

Procedure D was followed using (R)-4-phenyl-2-aminobutane (0 91 g, 6 1 mmol) (e e =98 2%) and 4-methylbenzaldehyde (0 73 g, 6 1 mmol) The reaction was completed in 7 days affording 1 44 g (94%) of the product with a purity of 99 8% (GLC) in 1 geometric isomer m p 60°C $[\alpha]_D^{20}$ = -109 1° (c=1, $CHCl_3$) Calc for $C_{18}H_{21}N$ (251 37) C 86 01, H 8 42, N 5 57, found C 85 10, H 8 43 N 5 54 % MS (EI) m/e 251 (M^+, 8%), 146 (M^+-$PhCH_2CH_2$, 100%), 119 (Me-$C_6H_4CH_2N^+$, 27%), 105 ($PhCH_2CH_2^+$, 12%), 91 ($PhCH_2^+$, 55%), 77 (Ph^+, 15%) ^{1}H-NMR (100 MHz in $CDCl_3$) δ 8 22 (s, 1H, N=C<u>H</u>), 7 69-7 61 (d, 2H, Ar<u>H</u>), 7 34-7 19 (m, 7H, Ar<u>H</u>), 3 32 (m, 1H, N-C<u>H</u>, J=6 4 Hz), 2 68-2 47 (m, 2H, PhC<u>H</u>$_2$), 2 36 (s, 3H, CH_3), 2 05-1 80 (m, 2H, $PhCH_2C\underline{H}_2$), 1 27 (d, 3H, C<u>H</u>$_3$, J=6 4 Hz) ppm ^{13}C-NMR (25 2 MHz in $CDCl_3$) δ 159 3 (C=N), 142 3-125 6 (aromatic C), 65 9 (N-<u>C</u>H), 39 3 ($Ph\underline{C}H_2$), 32 7 ($PhCH_2\underline{C}H_2$), 22 7 (CH_3), 21 5 ($Ph\underline{C}H_3$) ppm IR (CCl_4) ν=1644 (C=N) cm^{-1}

(R)-4-fluorobenzylidene-(1-methyl-3-phenyl-propyl)-amine (4e, R_1 = $PhCH_2CH_2$, R_2 = CH_3, X=F)

Procedure D was followed using (R)-4-phenyl-2-aminobutane (0 91 g, 6 1 mmol) (e e =98 2%) and 4-fluorobenzaldehyde (0 76 g, 6 1 mmol) The reaction was completed in 7 days affording 1 50 g (96%) of the product with a purity of 99 4% (GLC) in 1 geometric isomer $[\alpha]_D^{20}$ = -97 5° (c=1, $CHCl_3$) HRMS Calc for $C_{17}H_{18}NF$ 255 1423, found 255 1424 MS (EI) m/e 255 (M^+, 53%), 150 (M^+-$PhCH_2CH_2$, 100%), 91 ($PhCH_2^+$, 55%), 77 (Ph^+, 14%) ^{1}H-NMR (100 MHz in $CDCl_3$) δ 8 20 (s, 1H, N=C<u>H</u>), 7 80-7 62 (m, 2H, Ar<u>H</u>), 7 36-6 98 (m, 7H, Ar<u>H</u>), 3 31 (m, 1H, N-C<u>H</u>, J=6 3 Hz), 2 67-2 48 (m, 2H, PhC<u>H</u>$_2$), 2 04-1 80 (m, 2H, $PhCH_2C\underline{H}_2$), 1 26 (d, 3H, C<u>H</u>$_3$, J=6 3 Hz) ppm ^{13}C-NMR (25 2 MHz in $CDCl_3$) δ 169 2 (C=N), 159 2-115 2 (aromatic C), 65 8 (N-<u>C</u>H), 39 3 ($Ph\underline{C}H_2$), 32 7 ($PhCH_2\underline{C}H_2$), 22 7 (CH_3) ppm IR (CCl_4) ν=1640 (C=N) cm ^{1}

(R)-(benzylidene)-(1-phenyl-ethyl)-amine (5a, R_1 = Ph, R_2 = CH_3, X=H).

Procedure D was followed using R-(+)-α-methylbenzylamine (10 42 g, 10 0 ml, 98 0 mmol) (e e =96 0%) and benzaldehyde (11 94 g, 12 7 ml, 98 5 mmol) The reaction was completed in 7 days affording 19 0 g (93%) of the product with a purity of 99 6% (GLC) in 1 geometric isomer E e (%) 96 0% (HPLC n-hexane/2-propanol = 98 2) $[\alpha]_D^{20}$ -73 6° (c=1, $CHCl_3$) HRMS Calc for $C_{15}H_{15}N$ 209 2935 found 209 2934 MS (EI) m/e 209 (M^+, 100%), 194 (M^+-CH_3, 12 6%), 132 (M^+-C_6H_5, 3%), 105 ($C_6H_5C(CH_3)H^+$, 63%), 77 (Ph^+, 3%) ^{1}H-NMR (100 MHz in $CDCl_3$) δ 8 27 (s, 1H, imine <u>H</u>C=N), 7 79-7 12 (m, 10H, aromatic), 4 47 (q, 1H, J=6 6 Hz, benzylic H), 1 55 (d, 3H, J= 6 6 Hz, CH_3) ppm ^{13}C-NMR (25 2 MHz in $CDCl_3$) δ 159 5 (C=N), 145 3-126 7 (aromatic C), 69 6 ($C_6H_5\underline{C}HCH_3$), 25 1 (CH_3) ppm IR (CCl_4) ν=3100-3000 (aromatic), 2970- 2800 (alkyl), 1640 (C=N) cm^{-1}

(R)-(4-chloro-benzylidene)-(1-phenyl-ethyl)-amine (5b, R_1 = Ph, R_2 = CH_3, X=Cl).

Procedure D was followed using R-(+)-α-methylbenzylamine (0 79 g, 1 12 ml, 6 5 mmol) (e e =96 0%) and 4-chlorobenzaldehyde (0 90 g, 6 45 mmol) The reaction was completed in 7 days affording 1 51 g (90%) of the product with a purity of 99 6% (GLC) in 1 geometric isomer E e (%) 96 0% (HPLC n-hexane/2-propanol 98/2) m p 72°C $[\alpha]_D^{20}$: -85 7° (c=1, $CHCl_3$) Calc for $C_{15}H_{14}NCl$ (243 8) C 73 92, H 5 79, N 5 75%, found C 73 86, H 5 74, N 5 80% MS (EI) m/e 243 (M^+, 14 5%), 228 (M^+-CH_3, 8 5%), 166 (M^+-C_6H_5, 6 3%), 105 ($C_6H_5C(CH_3)H^+$, 100%), 77 ($C_6H_5^+$, 6 3%) ^{1}H-NMR (100 MHz in $CDCl_3$) δ 8 23 (s, 1H, imine <u>H</u>C=N), 7 67-7 13 (m, 9H, aromatic), 4 43 (q, 1H, J=7 Hz, benzylic H), 1 50 (d, 3H, J= 7 Hz, CH_3) ppm ^{13}C-NMR (25 2 MHz in $CDCl_3$) δ 157 7 (C=N), 144 9-126 5 (aromatic C), 69 7 ($C_6H_5\underline{C}HCH_3$), 24 9 (CH_3) ppm IR (KBr) ν=3100-3000 (aromatic), 2970- 2800 (alkyl), 1640 (C=N) cm^{-1}

(R)-(4-methyl-benzylidene)-(1-phenyl-ethyl)-amine (5d, R_1 = Ph, R_2 = CH_3, X=CH_3).

Procedure D was followed using R-(+)-α-methylbenzylamine (0 94 g, 1 00 ml, 7 8 mmol) (e e =96 0%) and 4-methylbenzaldehyde (0 93 g, 7 8 mmol) The reaction was completed in 7 days affording 1 74 g (99%) of the product with a purity of 99 7% (GLC) in 1 geometric isomer E e (%) 96 0% (HPLC n-hexane/2-propanol 98/2) m p 81°C (decomp) $[\alpha]_D^{20}$ -86 1° (c=1, $CHCl_3$) Calc for $C_{16}H_{17}N$ (223 32) C 86 05, H 7 67, N 6 27%, found C 85 84, H 7 75, N 6 25% MS (EI) m/e 223 (M^+, 2%), 208 (M^+-CH_3, 3%), 1105 ($C_6H_5C(CH_3)H^+$, 50%), 91 ($PhCH_2^+$, 100%), 77 ($C_6H_5^+$, 6%) ^{1}H-NMR (100 MHz in $CDCl_3$) δ 8 26 (s, 1H, imine <u>H</u>C=N), 7 64-7 10 (m, 9H, aromatic), 4 43 (q, 1H, J=6 7 Hz, benzylic H), 2 30 (s, 3H, $C_6H_4C\underline{H}_3$), 1 50 (d, 3H, J= 6 7 Hz, CH_3) ppm ^{13}C-NMR (25 2 MHz in $CDCl_3$) δ 159 4 (C=N), 144 9-126 6 (aromatic C), 69 9

($C_6H_5CHCH_3$), 24 7 (CH_3), 21 6 (PhCH$_3$) ppm IR (CCl_4) ν=3100-3000 (aromatic), 2970- 2800 (alkyl), 1640 (C=N) cm^{-1}

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Appendix

Kinetics, Thermodynamics, Hammett equations and Racemization analysis

First order equilibrium kinetics

In the following equation a first order equilibrium reaction is shown:

$$A \underset{k_1}{\overset{k_{-1}}{\rightleftharpoons}} B$$

In this equation k_1 and k_{-1} are the first order reaction rate constants for the forward and reverse reaction, respectively. The rate expression for the conversion of A reads:

$$-\frac{d[A]}{dt} = k_1[A] - k_{-1}[B] \qquad \text{A.1}$$

The conditions are:

1) $[A]_o$ = concentration of A at t=0, $[B]_o = 0$.
2) $[A]_{eq}$ = concentration of A at t= ∞, $[B]_{eq}$ = concentration of B at t= ∞
3) At equilibrium d[A]/dt = 0
4) $K_{eq} = k_1/k_{-1} = [B]_{eq}/[A]_{eq}$
5) $[A]_o - [A_t] = [B]_t$ A.2

Substitution of equation A.2 in A.1 gives equation A.3 in integration gives equation A.4[1].

$$-\frac{d[A]}{dt} = (k_1 + k_{-1})[A] - k_{-1}[A]_0 \qquad \text{A.3}$$

$$\ln\left\{\frac{k_1[A]_0}{(k_1 + k_{-1})[A]_t - k_{-1}[A]_0}\right\} = (k_1 + k_{-1})t \qquad \text{A.4}$$

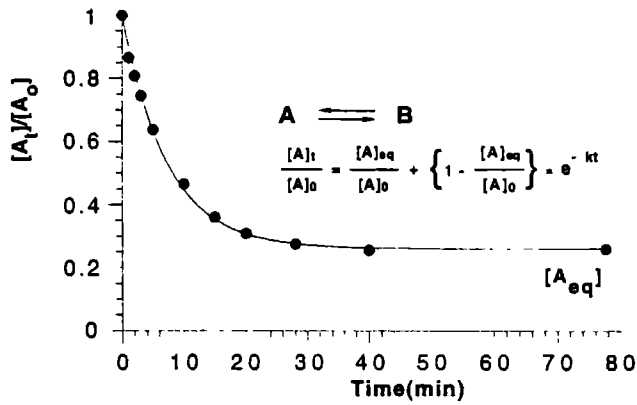
Reorganization of A.4 gives A.5 and A.6 which are useful for experimental analysis.

$$\ln\left\{\frac{[A]_0 - [A]_{eq}}{[A]_t - [A]_{eq}}\right\} = (k_1 + k_{-1})t \qquad \text{A.5}$$

$$\frac{[A]_t}{[A]_0} = \frac{[A]_{eq}}{[A]_0} + \left\{1 - \frac{[A]_{eq}}{[A]_0}\right\} * e^{-kt} \qquad \text{A.6}$$

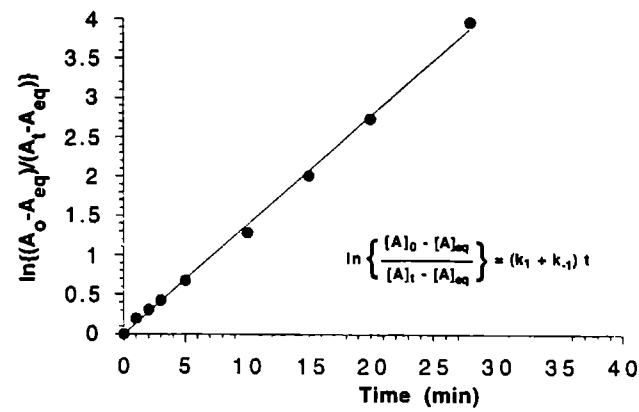
A plot of $[A]_t/[A]_0$ against time is given in Figure A.5.1. From this plot $[A]_{eq}$, K_{eq} and k_{exp} can be determined using fitting procedures.

Figure A.5.1 First order equilibrium kinetics in the imine isomerization reaction.



A plot based on equation A.5 is shown in Figure A.5.2, the slope of the straight line equals to (k_1+k_{-1}) or k_{exp}.

Figure A.5.2 Determination of rate constant k_{exp} of the imine isomerization reaction.

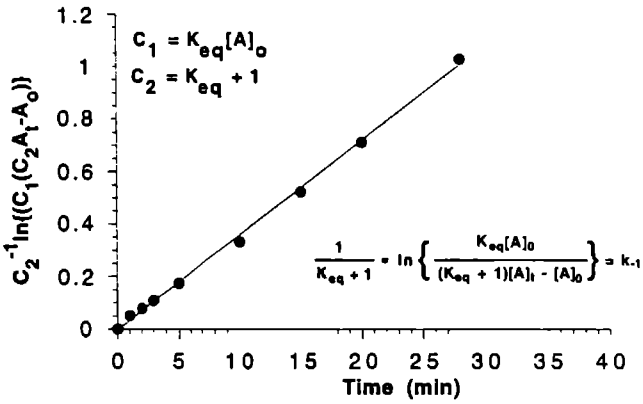


Substitution of $K_{eq}=k_1/k_{-1}$ in equation A.5 gives equation A.7.

$$\frac{1}{K_{eq}+1} * \ln\left\{\frac{K_{eq}[A]_0}{(K_{eq}+1)[A]_t - [A]_0}\right\} = k_{-1}t \qquad \text{A.7}$$

A plot derived from A.7 is shown in Figure A.5.3.

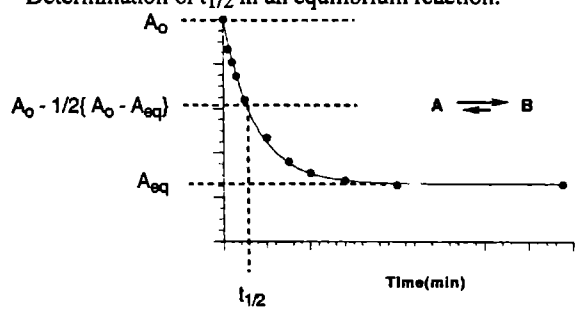
Figure A.5.3 Determination of k_{-1} of the imine isomerization reaction.



Substitution of the values of A_{eq} into A.5 and K_{eq} into A.7, respectively, allows the determination of rate constants k_1 and k_{-1}.

The half-life of an equilibrium reaction ($t_{1/2}$) is obtained from a plot of the concentration of A against time (Figure A.5.4).

Figure A.5.4 Determination of $t_{1/2}$ in an equilibrium reaction.



Equation A.8 can be derived from A.5 by substitution of $\{[A_o] - 1/2\{[A_o] - [A_{eq}]\}$ at $t_{1/2}$ giving:

$$t_{1/2} = \frac{1}{k_1 + k_{-1}} * \ln (2) \qquad \text{A.8}$$

There are two significant features about this equation. One is that $t_{1/2}$ may readily be determined from a plot of $[A]_t$, against time and therefore this is a very fast method to determine the overall first order equilibrium rate constant k_{exp}. The other is that $t_{1/2}$ of a first order equilibrium reaction is independent of the concentration of the reactants.

The use of the turnover frequency (TOF) or turnover number (TO-number) is another possibility to define the rate of a reaction in catalytic processes. The TO-number is defined as the molar amount of reaction product obtained per mol catalyst per hour. For equilibrium reactions the TO-number decreases continuously during the reaction and eventually becomes zero when equilibrium is reached. Therefore, initial TO-numbers were calculated for the imine isomerization reactions. At time t = 0 the concentration of A equals $[A]_0$ and the concentration of B equals zero, which simplifies equation A.1 and equation A.9 can be derived.

$$-\frac{d[A]_{t=0}}{dt} = k_1[A]_o \qquad \text{A.9}$$

The TO-number is defined as

$$\text{TO-number} = \frac{d[A]}{dt} * \frac{1}{[\text{catalyst}]} \qquad \text{A.10}$$

Substitution of A 9 in A 10 gives equation A 11 and the initial TO-number is only dependent on the reaction constant for the forward reaction (k_1)

$$\text{TO-number}_{t=o} = \frac{k_1 * [A]_0}{[\text{catalyst}]} \qquad \text{A.11}$$

In most imine isomerization experiments the concentration of the imine substrate and the catalyst are 1 0 mol/l and 0 3 mol/l, respectively After substitution of these values equation A 12 is obtained

$$\text{TO-number}_{t=0} = 200 * k_1\ \text{min}^{-1} \qquad \text{A.12}$$

Relevant formulae for ΔG, ΔH and ΔS are A 13, A 14 and A 15, where ΔG, ΔH and ΔS are the linear free Gibbs energy, the enthalpy and the entropy, respectively

$$\Delta G = \Delta H - T\Delta S \qquad \text{A.13}$$

$$\Delta G = - RT \cdot \ln K_{eq} \qquad \text{A.14}$$

Substitution of equation A 13 in A 14 gives

$$\ln[K_{eq}] = -\frac{\Delta H}{R} * \frac{1}{T} + \frac{\Delta S}{R} \qquad \text{A.15}$$

A plot of $\ln(K_{eq})$ against 1/T gives a straight line, the slope equals to -ΔH/R and the intercept equals to ΔS/R The values of ΔH and ΔS give information about the relative energy states of the reactants and products compared to each other in a chemical reaction In order to occur spontaneously, a chemical reaction product must have a lower linear free energy value than the reactant ($\Delta G < 0$) The enthalpy change gives information on the binding energy differences between reactant and product The entropy change is used to obtain information on the mobility and flexibility of a reactant and its product before and after the reaction A highly mobile and more flexible reaction product ($\Delta S > 0$) has a positive effect on the reaction In most chemical reactions, however, the enthalpy change is dominant over the entropy change and therefore most chemical reactions are enthalpy driven

Eyring and Arrhenius analysis of the reaction constants (k_1, k_{-1})

There are essentially two methods to obtain information about the energy profile of a chemical equilibrium reaction. The first method (empirical) uses the Arrhenius equation[2] A.16, which can also be reorganized into another form A.17.

$$k_{obs} = A \cdot \exp(-E_a/RT) \qquad \text{A.16}$$

$$E_a = -RT \cdot \ln(k_{obs}/A) \qquad \text{A.17}$$

By plotting $\ln(k_{exp})$ against 1/T the slope of the straight line equals to $-(E_a/R)$, and the activation energy of the reaction of interest can be determined using A.17

The second method is based on the transition state theory for which formula A.18 can be derived,[3] where k_B, T, h, $\Delta G^{\neq}$, $\Delta H^{\neq}$, $\Delta S^{\neq}$ and R are the Boltzmann constant, the absolute temperature, the Planck constant , the standard Gibbs energy of activation , the standard enthalpy of activation , the standard entropy of activation , and the gas constant R, respectively.

$$k_1 = \frac{k_B T}{h} \exp\left(-\frac{\Delta G^{\neq}}{RT}\right) = \frac{k_B T}{h} \exp\left(-\frac{\Delta H^{\neq}}{RT}\right) \exp\left(\frac{\Delta S^{\neq}}{R}\right) \qquad \text{A.18}$$

On reorganization A.19 is obtained, which can be used to analyze experimental results.

$$\ln\left(\frac{k_1}{T}\right) = -\frac{\Delta H^{\neq}}{R} \cdot \frac{1}{T} + \frac{\Delta S^{\neq}}{R} + \ln\left(\frac{k_B}{h}\right) \qquad \text{A.19}$$

By plotting of $\ln(k_1/T)$ against 1/T the slope of the straight line equals to $-\Delta H^{\neq}/R$ and the intercept equals to $(\Delta S^{\neq}/R + \ln(k_B/h))$. From the partial derivatives of equations A 17 and A 19 $(\partial(\ln k/\partial t))$ equation A.20, can be obtained.

$$E_a = \Delta H^{\#} + RT \qquad \text{A.20}$$

At room temperature (T=298K) the difference between $\Delta H^{\#}$ and E_a amounts to 2.5 kJ/mol

Hammett analysis

For the evaluation of the substituent effect on reaction rates and equilibrium, the Hammett relationship[4] is appropriate. The following expressions are relevant:

$$\log(k) = \log(k_o) + \rho\sigma$$
$$\log(K) = \log(K_o) + \rho\sigma$$

The values k_o or K_o are the values as determined for the unsubstituted 'parent' compound (*p*-H substituent).

Table 5.1 Hammett *para*-substituent constants for X = H, Cl, Me, OMe, F

X=	σ_p	σ^-_p	σ^+_p
H	0 00	0 00	0 00
Cl	0 23	0 19	0 11
p-Me	-0 17	-0 17	-0 31
p-OMe	-0 27	-0 26	-0 78
F	0 06	-0 03	-0 07

The substituent constant, σ, measures the polar effect of the substituent in a given position (*meta* or *para*), relative to hydrogen and is independent of the nature of the reaction The Hammett reaction constant, ρ, depends on the nature of the reaction, including conditions such as solvent and temperature, and measures the susceptibility of the reaction to polar effects A reaction which is facilitated by reducing the electron density at the reaction center has a positive ρ–value whereas an increase of the electron density at the reaction center corresponds with a negative ρ–value The ρ scale covers roughly 0±4

The first refinement of the Hammett equation makes use of σ^+ and σ^- values in stead of σ, which are appropriate in reactions in which extensive electron delocalization is present [5] The σ^+, σ^- and σ-values for several *para*-substituents are shown in Table 5 1

Racemization analysis

For first order equilibrium racemization reactions the expressions A 21, A 22, A 23, A 24, A 25 and A 26 are of importance [6]

$$R \underset{k_S}{\overset{k_R}{\rightleftharpoons}} S \qquad k_R = k_S = k_{rac} \qquad \text{A.21}$$

In A 21 k_R and k_S are the first order reaction rate constants for conversion of the R enantiomer into the S enantiomer and vice versa The value of k_R is equal to k_S and and can also be defined as k_{rac}

$$-\frac{d[R]}{dt} = k_{rac}[R] - k_{rac}[S] = k_{rac}\{[R] - [S]\} \qquad \text{A.22}$$

1) $[R]_o$ is the concentration of R at t = 0, whereby [S] = 0
2) $[R]_o - [R] = [S]$ **A 23**

By inserting A 23 into A 22 equation A 24 is obtained, which can be integrated directly giving equation A 25

$$-\frac{d[R]}{dt} = 2k[R] - [R]_o = 2k\{[R] - 1/2\,[R]_o \qquad \text{A.24}$$

$$\ln\{2[R] - [R]_o\} = \ln [R]_o - 2k_{rac}t \qquad \text{A.25}$$

The enantiomeric excess is defined in A 26

$$E.E = [R] - [S] = [R] - \{[R]_o - [R]\} = 2[R] - [R]_o \qquad \text{A.26}$$

Substitution of A 25 in A 26 gives A 27

$$\ln \{ \text{E.E.} \} = \ln \{\text{E.E.}\}_o - 2k_{rac}t \qquad \text{A.27}$$

If ln[e e.(%)] is plotted against time the gradient equals $-2k_{rac}$, and the value of k_{rac} can be calculated The factor 2 in A.27 can be accounted for as follows. When one R enantiomer is converted into an S enantiomer two molecules are turned into a racemic pair of molecules The generated S enantiomer will form a racemic pair with another R enantiomer, in this way neutralising the optical activity of two molecules

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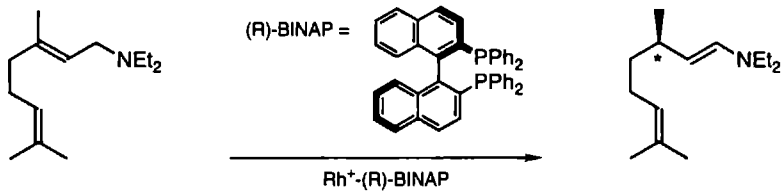
Catalytic Enantioselective Synthesis of Chiral Amines via the Asymmetric Imine Isomerization Reaction

6.1 Introduction

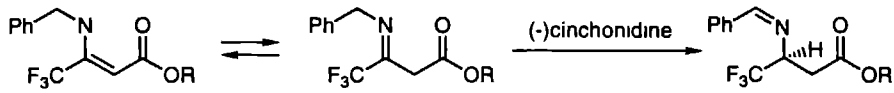
From the viewpoint of industrial utilization, the real breakthrough in catalytic asymmetric synthesis was the discovery of the Rh-BINAP catalyzed enantioselective isomerization of prochiral allylic amines. This reaction is based on an asymmetric olefinic double bond isomerization using a transition metal catalyst.[1] The highly efficient catalytic asymmetric isomerization of diethylgeranylamine into citronellaldiethylamine, is depicted in Scheme 6.1.



Scheme 6.1.

Since 1983 Takasago International Corporation manufactures L-menthol on a commercial scale using this asymmetric isomerization process[2] in the key step. The process is currently used for the production of about 2000 tons L-menthol per year, making it by far the most important example of industrial catalytic asymmetric synthesis.

An alternative for the transition metal catalyst induced asymmetric isomerization reactions is the base catalyzed asymmetric rearrangement of unsaturated systems, which involve a reshuffling of hydrogen atoms and double bonds in an asymmetric fashion (Schemes 6.2 and 6.3)

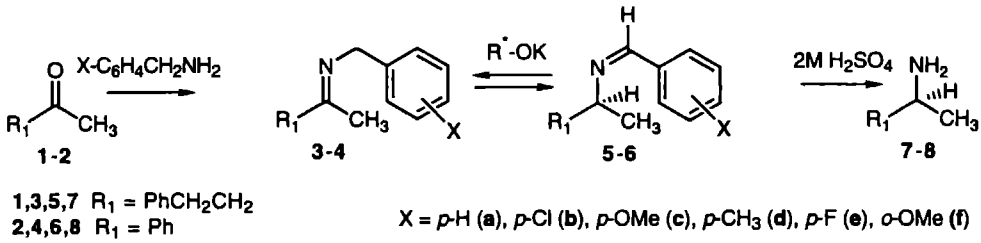


Scheme 6.2.

Much effort has been devoted to the elucidation of the mechanism of this [1,3]-proton shift reaction by Ingold et al.[3] in the 1930s, by Ossorio et al.[4] in the 1950s and by Cram et al.[5] in the 1960-70s using achiral bases. A brief survey on this subject is given in chapter 2. In chapter 5 the isomerization of imines derived from benzylacetone, acetophenone, and benzophenone was studied by means of a kinetic analysis. From these results additional evidence for the aza-allylic anion mechanism as proposed by Cram was obtained.

An asymmetric version of the imine isomerization (methylene azomethine rearrangement) using chiral bases has been reported for the first time by Soloshonok et al.[6] in 1994 (Scheme 6.2)

and shortly thereafter by the author of this thesis (1995) in a preliminary communication[7] (Scheme 6.3).



Scheme 6.3.

This chapter deals with the enantioselective [1,3]-proton transfer in the aza-allylic system of *N*-benzylimines **3-4** catalyzed by chiral bases, which results in the formation of thermodynamically favored *N*-benzylidene derivatives **5-6**. The synthesis of enantiomerically enriched amines **7-8** starting from prochiral ketones **1-2** could be achieved using this methodology (Scheme 6.3).

6.2 Results and Discussion

6.2.1 Catalysts

Chiral lithium amides have been applied in asymmetric synthesis for a long time and important applications of this class of reagents have been described.[8] It turned out that chiral lithium amide bases were not successful as catalysts in the imine isomerization reaction of model imines **3b** (X=Cl) and **4a** (X=H) Under the influence of the lithium amide bases the imines **3b** and **4a** were deprotonated, as was concluded from the dark red color of the reaction mixture, but no isomerization reaction was observed.

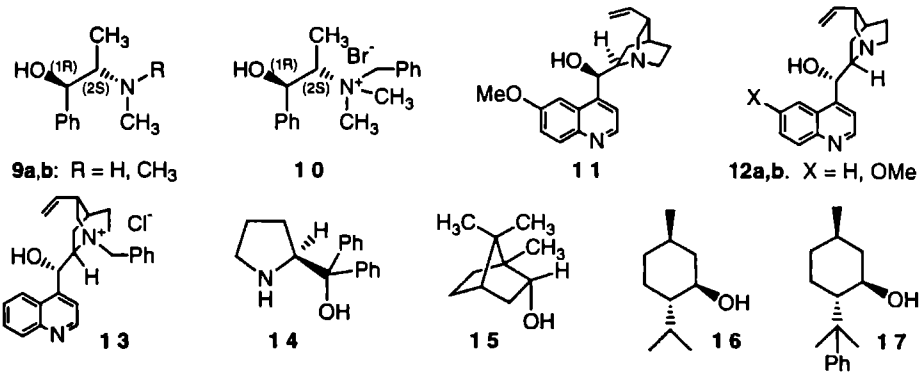
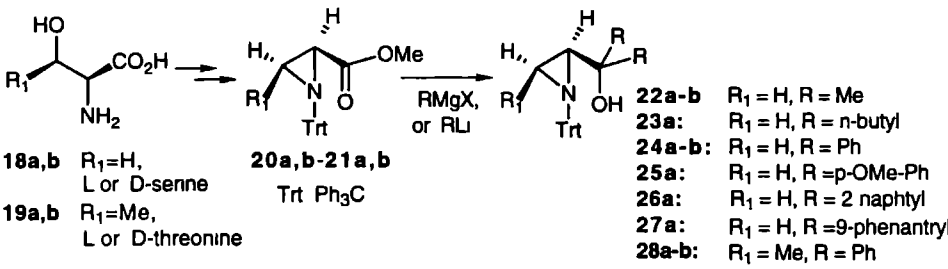


Figure 6.1

However, the isomerization reaction could be performed when potassium alkoxide catalysts derived from chiral alcohols and amino alcohols were employed. Until now, the use of chiral alkoxides as catalysts in asymmetric reactions has scarcely been reported.[9] Some of the chiral alcohols and amino alcohols used are commercially available, *viz* (-)-ephedrine (**9a**), (-)-*N*-methylephedrine (**9b**), (-)-*N*-benzyl-*N*-methylephedrinium bromide (**10**), quinine (**11**), cinchonine (**12a**), quinidine (**12b**), *N*-benzyl-cinchoninium chloride (**13**), (S)-α,α-diphenyl-2-

pyrrolidinemethanol (**14**), L(-)-borneol (**15**), L(-)-menthol (**16**) and L(-)-8-phenylmenthol (**17**) (Figure 6 1)

In a research project dealing with the asymmetric catalytic reduction of prochiral ketones a new class of chiral catalysts derived from aziridine-2-carboxylic esters[10] was introduced (chapters 3 and 4) For this purpose a convenient multigram 'one-pot procedure' of the synthesis of the *N*-trityl-aziridine-2-carboxylic esters (**20,21**) from *N*-trityl-serine and threonine methyl esters (**18,19**) was developed A subsequent Grignard reaction or addition of alkyllithium gave *N*-trityl-aziridine-2-dialkyl or aryl alcohols (**22-28**)[11] (Scheme 6 4)



Scheme 6 4

The R groups in the Grignard or R-Li reagents were varied in an attempt toward catalyst performance optimization in both the asymmetric catalytic reduction and isomerization reaction The methyl, *n*-butyl, phenyl, *p*-OMe-phenyl, and naphtyl groups were chosen as R groups The crude aziridine-2-tertiairy alcohols **22-28** were isolated and purified by flash column chromatography followed by recrystallization yielding enantiomerically pure **22-28** in 60-80% (Table 6 1) The e e 's of the protected aziridine-2-tertiary alcohols **22-28** were determined by HPLC analysis using a chiral column (Chiralcel OD) and were higher than 97% in all cases, implying that during the aziridine-2-tertiairy alcohol syntheses no racemization occurred

Table 6.1 Yields, optical rotation values, and e e 's of the *N*-trityl-aziridine carbinols **22-28**

Derivative of aminoacid:	Compound	R	$[\alpha]_D^{20}$ (c=1; $CHCl_3$)	Yield (%)	e.e. (%)[c]
L-Serine	**22a**	Me	+28 2°	(92)[a] 80[b]	97
D-Serine	**22b**	Me	-32 2°	(92)[a] 80[b]	98
L-Serine	**23a**	n-butyl	-16 2°	55[b]	98
L-Serine	**24a**	Ph	-78 8°	(92)[a] 62[b]	>99
D-Serine	**24b**	Ph	+82 8°	(86)[a] 68[b]	>99
L-Serine	**25a**	p-OMe-Ph	-107 0°	68[b]	>99
L-Serine	**26a**	2-naphtyl	-128 6°	50[b]	>99
L-Serine	**27a**	9-phenantryl	-102 0°	35[b]	>99
L-Threonine	**28a**	Ph	+22 5°	76[b]	>99
D-Threonine	**28b**	Ph	-22 2°	72[b]	>99

a) Crude yield b) After purification by flash column chromatography and recrystallization c) E e - determination using HPLC (Chiralcel OD, hexane/2 propanol 90/10)

(-)-*N*-Trityl-ephedrine (**29**) was prepared from commercially available (-)-ephedrine, whilst (2S)-aziridin-2-yl-diphenylmethanol (**30a**) was obtained by deprotection of **24a** (chapter 4) Attempts to prepare (S)-*N*-trityl-α,α-dimethyl-2-pyrrolidine methanol from commercially available (S)-α,α-diphenyl-2-pyrrolidine methanol (**14**) were not successful The chiral amino alcohols (S)-

N-methyl-α,α-dimethyl-2-pyrrolidine methanol (**31**),[12] α,α,α',α'-tetramethyl (phenyl)-1,3-dioxolan-4,5-dimethanol (**32-33**)[13] and *N*-α-methyl benzylamine protected azetidine-2-carbinol (**34**)[14] were prepared according to literature procedures (Figure 6.2).

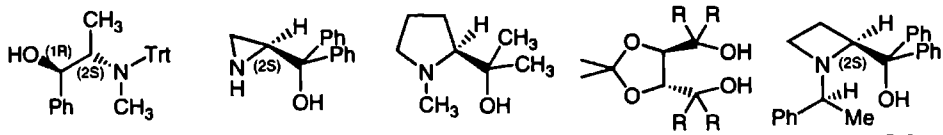


Figure 6.2

6.2.2 Asymmetric imine isomerization reactions

The enantioselective [1,3]-proton transfer in the aza-allylic system of *N*-benzylimines **3b** and **4a** catalyzed by chiral bases (**9-34**), leading to the thermodynamically favored chiral *N*-benzylidene derivatives **5b** and **6a** are described in this section (Scheme 6.3).

Table 6.2 Asymmetric isomerization of imine **3b** (R_1 = $PhCH_2CH_2$) using chiral potassium alcoholates derived from **9-31**

Entry	Reaction Conditions[a]			K_{eq}	TO	$t_{1/2}$ min[b]	e.e.$_{max}$ (%)[c]
	Base	Solvent	Temp,°C	(C_{max})[n]	number[l]		(Config)[c]
1	**9b**[d]	THF	66	(79)	2.4	45[k]	12 (S)
2	**9b**	THF	66	(70)	1.5	60[k]	7 (R)
3	**9b**	toluene	105	(77)	0.24	450[k]	10 (R)
4	**9b**[e]	THF	66	5.53	1.6	24	7 (S)
5	**11**	THF	66	5.51	3.6	33	8 (R)
6	**12b**	THF	66	5.50	4.3	27	9 (S)
7	**15**[j]	THF	22	8.65	0.81	48.5	2 (S)
8	**16**[h]	THF	22	8.55	3.3	19	3 (S)
9	**16**	toluene	90	4.38	2.7	42	3 (S)
10	**17**[i]	THF	66	5.49	16.1	11	2 (S)
11	**24a**	THF	66	(70)	1.3	90[k]	22 (S)
12	**24a**[f]	THF	66	(72)	1.1	100[k]	18.5 (S)
13	**24a**[g]	THF	66	(21)	1.4	90[k]	17 (S)
14	**24a**	toluene	105	(62)	0.31	320[k]	44 (S)
15	**28a**	THF	66	(41)	0.52	105[k]	2 (S)
16	**28a**	toluene	105	(50)	0.27	300[k]	7 (S)
17	**29**	toluene	105	(61)	0.21	375[k]	2 (R)
18	**31**	THF	20	8.67	1.0	123	3 (R)
19	**31**	THF	66	5.43	19	6.2	1.5 (R)

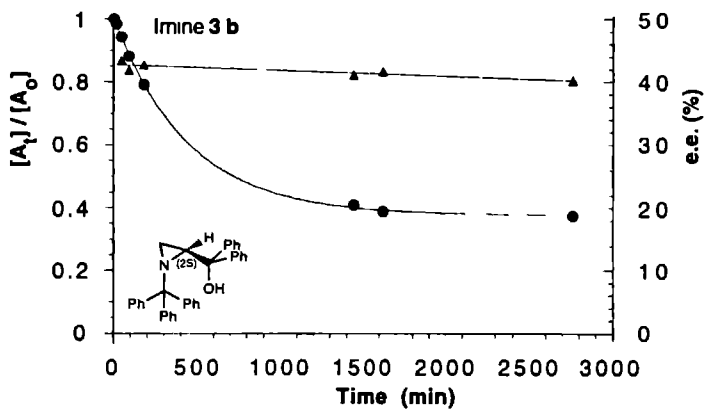
a) Concentration of potassium salt of catalysts **9-31** is 30 mol % and the imine concentration is 0.2 mmol/mL b) The parameter $t_{1/2}$ is the reaction time for 50% conversion of the starting material as determined from the conversion versus time plot c) E.e. of **3a** determined by HPLC (Daicel Chiralpak AD) (eluent: hexane/2-propanol 98/2, v/v). d) (+)-*N*-Methylephedrine was used. e) [**9b**] = 95 mol % and (+)-*N*-Methylephedrine was used f) [**24a**] = 24 mol %. g) [**24a**] = 15 mol % h) [**16**] = 60 mol % i) [**17**] = 20 mol %. j) [**15**] = 95 mol % k) no equilibrium is reached l) TO-number = turnover number and is defined as mol product / mol catalyst / hour at t = 0. n) C_{max} = maximum conversion (%) of starting material.

All imine isomerization reactions were performed in THF or toluene in the presence of 30 mol (%) of chiral alcoholate catalyst. These chiral catalysts were obtained by treatment of the

corresponding alcohols **9-34** with 1 equivalent of KH in THF or toluene for 60 min. at 70°C. Subsequently, the imine substrates **3b** and **4a** were added. The reactions were monitored using GLC and HPLC[15] and the percentage of conversion and the e.e.'s were followed during the process of the reaction.

The results for the isomerization of imine **3b** into **5b** using chiral alkoxides derived from **9-31** are collected in Table 6.2. These data reveal that in THF asymmetric induction could be achieved for the isomerization of **3b** into **5b**. When the reactions were performed in the apolar solvent toluene the rate of the imine isomerization decreased, whereas the asymmetric induction increased in almost all cases. The imine isomerization rate increases at higher temperatures, as was concluded from experiments using model imine **3b** and catalyst **31** in THF at 20°C and 66°C, respectively (entry 18-19). In most cases, rather high reaction temperatures were needed for the imine isomerization of **3b** into **5b** to occur. Therefore, most imine isomerization reactions of imine **3b** were performed at 66°C in THF and at 105°C in toluene. The data in Table 6.2 show that the highest enantioselectivities were obtained with the chiral potassium alkoxide derived from *N*-trityl-aziridine-2-yl-diphenylmethanol (**24a**) (17-44%, entry 11-14). When the chiral catalyst derived from L-threonine **28a** was used, the enantioselectivity was disappointingly low (e.e = 2-7%, entry 15-16). These results indicate that small changes in the catalyst structure, e.g. a *cis* methyl group (catalyst **28a**) in stead of a *cis* hydrogen atom (catalyst **24a**), have a substantial influence on the asymmetric induction during the imine isomerization reaction.

Figure 6.3 Asymmetric imine isomerization of imine **3b** using the chiral potassium alcoholate derived from **24a** as the catalyst



● $[A_t] / [A_0]$ = 100 - conversion (%) / 100 measured by GLC and ▲ E.e (%) = enantiomeric excess of **5b** measured by HPLC as a function of time. Reaction conditions: [imine **3b**] = 0.2 mmol/mL, [catalyst **24a**] = 0.06 mmol/mL (0.3 equiv), solvent: toluene, temperature. 105°C.

The second best catalyst in this reaction was *N*-methyl ephedrine (**9b**) (e.e = 7-12%, entry 1-4). The (S)- and (R)-imines and their corresponding (S)- and (R)-amines could be prepared using the potassium alkoxide catalyst from (+)-*N*-methylephedrine (entry 1, 4) and (-)-*N*-methylephedrine (entry 2, 3). With the pseudo-enantiomeric catalysts derived from quinine (**11**) and quinidine (**12b**) (R)- and (S)-imines could be obtained, respectively, but the e.e's were low (e.e=8-9%, entry 5-6). From these results it was concluded that the cinchona alkaloid catalysts, which have proven to be excellent catalysts in several asymmetric reactions,[16] are not the catalysts of choice for the asymmetric imine isomerization reaction.

The influence of the catalyst concentration on the enantioselectivity of the asymmetric imine isomerization reaction is marginal. For catalysts **9b** (entry 1, 4), **16** (entry 8, 9), and **24a** (entry

Table 6.3 Asymmetric isomerization of imine **4a** (R_1 = Ph) using chiral potassium alcoholates derived from **9-34**

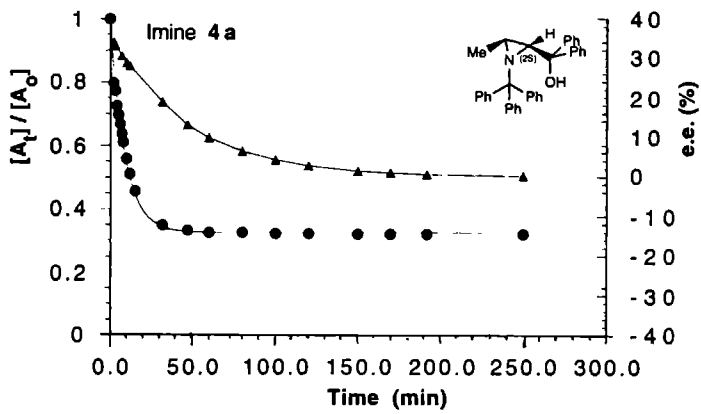
Entry	Reaction Conditions[a]			K_{eq}	k_{exp}	k_1	k_{-1}	k_{rac}	k_{-1}/k_{rac}	TO number[b]	$t_{1/2}$ min[c]	e.e.$_{max}$ (%)[d] (Config)
	Base	Solvent	Temp,°C									
1	**9b**	toluene	20	2.12	172.1	116.9	55.2	19.5	2.8	23 4	4.0	6 (R)
2	**10**[g]	toluene	20	--	--	--	--	--	--	12.8	9	11 (R)
3	**11**	toluene	20	2.15	12.6	8.6	4.0	1.5	2.7	1.72	55	11 (S)
4	**13**	toluene	20	2.09	17.6	11.9	5.7	3.1	1.8	2.38	39	17 (S)
5	**14**[f]	toluene	20	2.20	6.4	4.4	2.0	1.1	1.8	0.88	108	6 (R)
6	**16**[e]	toluene	20	2.19	174.1	119.6	54.5	--	--	23.9	3.9	2 (S)
7	**16**[e,f]	toluene	20	2.22	58.0	40.0	18.0	6.6	2.7	8.0	12	6 (S)
8	**22a**[f]	toluene	23	2.03	92.8	62.1	30.6	7.3	4.2	12.4	7.5	15 (R)
9	**24a**	THF	66	2.00	442.2	294.3	147.9	--	--	58 9	1.6	1 (R)
10	**24a**	toluene	20	2.19	96.6	66.3	30.3	11.2	2.7	13.3	7.2	14 (R)
11	**24a**[f]	toluene	20	2.03	38.8	26.0	12.8	1.58	8.1	5.2	18	14 (R)
12	**24b**[h]	toluene	20	2.03	71.0	47.6	23.4	4.13	5.7	9.5	9.8	14 (S)
13	**25a**	toluene	20	2.03	54.2	36.3	17.9	4.4	4.1	7.3	12.8	11 (R)
14	**26a**[f]	toluene	24	2.21	12.2	8.4	3.8	0.9	4.2	1.7	57	16 (R)
15	**28a**[f]	toluene	24	2.03	106.2	71.2	35.0	10.6	5.2	14.2	6	34 (R)
16	**29**	toluene	20	2.16	39.2	26.8	12.4	4.3	2.9	5.4	17.7	13 (R)
17	**29**[f]	toluene	20	2.04	8.5	5.7	2.8	0.9	3.1	1.1	82	13 (R)
18	**30a**[f]	toluene	24	2.09	3.4	2.3	1.1	--	--	0.46	204	3 (R)
19	**32**[f]	toluene	23	2.19	42.4	29.1	13.3	4.9	2.7	5.8	16	4 (R)
20	**34**[f]	toluene	27	2.09	312.4	211.3	101.1	38.4	2.6	42.3	2.2	28 (S)

a) Concentration of potassium salt of catalysts **9-34** is 30 mol % and the imine concentration is 0 2 mmol/mL b) TO-number = turnover number and is defined as mol product / mol catalyst / hour at t = 0. c) The parameter $t_{1/2}$ is the reaction time for 50% conversion of the starting material d) E e of **6a** determined by HPLC (Daicel Chiralpak AD) (eluent. hexane / 2-propanol = 99 . 1, v/v). e) D(+)-Menthol was used f) [imine] = 0 1 mmol/mL g) Equilibrium is not reached h) (2R)- Diphenyl-(N-trityl-aziridine-2yl)-methanol was used.

11-13), the concentration was varied, resulting in a somewhat faster isomerization reaction at higher catalyst concentrations.

A typical example of a conversion versus time and e.e. versus time plot for the asymmetric imine isomerization of **3b** using the potassium alcoholate derived from **24a** in toluene is shown in Figure 6.3. From this plot it can be concluded that almost no racemization occurs during the asymmetric isomerization under the reaction conditions applied. In the case of an equilibrium reaction racemization of the product imine **5b** would be expected. The fact that no racemization is observed is explained by a deactivation of the catalyst during the isomerization process. Extra evidence for catalyst degradation during the reaction of imine **3b** was obtained from experiments using different concentrations of catalyst **24a** (entry 11-13). At lower catalyst concentrations lower conversions of imine **3b<=>5b** were obtained, implying that an equilibrium in the isomerization of imines **3b<=>5b** was never reached. Therefore, the reactions cannot be described by first order equilibrium kinetics and only $t_{1/2}$ and TO-numbers could be determined for this model system (Table 6.2).

Figure 6.4 Asymmetric imine isomerization of imine **4a** using chiral potassium alcoholate derived from **28a**.



● $[A_t] / [A_0]$ = 100 - conversion (%) / 100 measured by GLC or HPLC and ▲ e.e (%) = enantiomeric excess of **6a** measured by HPLC as a function of time. Reaction conditions: [imine **4a**] = 0.2 mmol/mL, [catalyst **28a**] = 0.06 mmol/mL (0.3 equiv), solvent: toluene, temperature: 22°C.

The results of the isomerization of imine **4a** into **6a** using chiral alkoxides are collected in Table 6.3. A fast imine isomerization of **4a** into **6a** was observed in THF, but no asymmetric induction could be achieved. When the reactions were performed in the apolar solvent toluene, an enantioselective imine isomerization reaction was accomplished in all cases. Table 6.3 reveals that maximum enantioselectivity is reached, when the chiral potassium alkoxide derived from *N*-trityl-3-methyl-aziridin-2-yl-diphenylmethanol (**28a**) was used (34%, entry 17-18). The enantioselectivity was lower (e.e = 14%, entry 18-19), when the chiral catalyst derived from L-serine **24a** was applied. Again it was found that small changes in the catalyst, a *cis* methyl group (catalyst **28a**) in stead of a *cis* hydrogen atom (catalyst **24a**), have a large influence on the asymmetric induction in the imine isomerization reaction. The preparation of (S)- and (R)-imines and their corresponding (S)- and (R)-amines using the potassium alkoxide catalyst from (2S)-**24a** (e.e. = 14%, entry 10) and (2R)-**24b** (e.e = 14%, entry 12) was successful. The second best catalyst in this reaction was *N*-trityl ephedrine (**29**) (e.e =13%, entry 2). Using the catalyst derived from quinine (**11**) (S)-imines were obtained, but the e.e's were relatively low (e.e = 11%, entry

3). These results are comparable with those for imine **3b** and again show that cinchona alkaloid catalysts are not the catalysts of choice in the asymmetric imine isomerization reaction.

In an attempt to increase the interaction of the aza-allyl anion intermediate and the chiral alkoxide catalysts the use of chiral quarternary ammonium salts was proposed. Numerous examples of the use of chiral phase transfer catalysts in enantioselective reactions have been described, but only a few reactions resulted in high enantioselectivities.[17] In the enantioselective isomerization reaction of prochiral imine **4a** (-)-*N*-benzyl-*N*-methylephedrinium bromide (**10**) and *N*-benzyl-cinchoninium chloride (**13**) were applied. The results in Table 6.3 indicate that a slight increase in enantioselectivity is observed for the quarternary ammonium catalysts **10** and **13** as compared to their corresponding potassium salt precursors **9b** and **11** (entries 1-4). For catalyst **10** the isomerization reaction of imine **4a** into **6a** did not reach equilibrium. This can be explained by the instability of the quarternary ammonium alkoxide derived from **10** under the basic reaction conditions used, and the relative ease by which it undergoes an intramolecular ring closure reaction to form dimethylbenzylamine and 1-phenyl-2-methyloxirane.

A typical example of a conversion versus time and e.e. versus time plot for the asymmetric imine isomerization of **4a** using the potassium alcoholate derived from **28a** in toluene is shown in Figure 6.4. The imine isomerization reaction can be described by first order equilibrium kinetics (appendix chapter 5) and K_{eq}, $k_{overall}$, k_1, k_{-1} and k_{-rac}-values were determined from the collected data. The results in Table 6.3 indicate that the values of k_{-1} and k_{rac} are different in all cases. This implies the presence of a reaction intermediate (aza-allyl anion) during the isomerization reaction and consequently a concerted process can be rejected.

6.2.3 New aziridine-2-carbinol catalysts

The highest enantioselectivities in the imine isomerization reaction were observed for the aziridine-2-carbinols derived from serine (**22-27**) and threonine (**28**). In an attempt to improve the catalyst performance it was of interest to investigate the effect of a variation of the R groups of the aziridine alcohols. The results in Table 6.4 indicate that a variation of the R-groups has a small influence on the asymmetric induction of the isomerization process. However, a comparison of the catalytic ability of aziridine carbinol catalyst **24a** and the corresponding detritylated catalyst **30a** shows an increase in the enantioselectivity as well as the isomerization reaction rate when the trityl group is present (Entries 4 and 8, Table 6.4).

Table 6.4 Asymmetric imine isomerization of imine **2b** (R_1 = Ph) using chiral potassium alcoholates derived from **22-30**

Entry	Reaction Conditions[a]			K_{eq}	TO number[d]	$t_{1/2}$ min[b]	e.e.$_{max}$ (%)[c] (Config)[c]
	Base	Solvent	Temp,°C				
1	**22a**[e]	toluene	24	2.03	12.4	7.5	15 (R)
2	**24a**	toluene	20	2.19	13.3	7.2	14 (R)
3	**24a**[e]	toluene	24	2.03	5.2	18	14 (R)
4	**24b**	toluene	20	2.03	9.5	9.8	14 (S)
5	**25a**	toluene	20	2.03	7.3	12.8	11 (R)
6	**26a**[e]	toluene	24	2.21	1.7	57	16 (R)
7	**28a**[e]	toluene	24	2.03	14.2	6	34 (R)
8	**30a**[e]	toluene	24	2.09	0.46	204	3 (R)

a) Concentration of potassium salt of catalysts **22-30** is 30 mol % and the imine concentration is 0.2 mmol/mL. b) The parameter $t_{1/2}$ is the reaction time for 50% conversion of the starting material; The method of calculation is described in the appendix in chapter 5. c) E.e. of **3b** determined by HPLC (Daicel Chiralpak AD) (eluent: hexane / 2-propanol = 99 : 1, v/v). d) TO-number = turnover number and is defined as mol product / mol catalyst / hour at t = 0. e) [Imine] = 0.1 mmol/mL.

Thus, the trityl group in catalysts **22-28** is important and therefore (-)-*N*-tritylephedrine (**29**) was prepared from (-)-ephedrine. The maximum e.e.'s in the isomerization of **4a** using amino alcoholates derived from **29** and **24a** were in the same range (14%, entries 10-16, Table 6.3). This is in contrast with the isomerization of imine **3b** using **29**, which led to a remarkable decrease in enantioselectivity (2%, entry 17, Table 6.2) as compared to the enantioselectivity obtained for **24a**. Apparently, the enantioselectivity is both substrate and catalyst dependent.

The presence of a free NH-group in the catalyst has a negative effect on the enantioselectivity and the reaction rate of the imine isomerization reaction of **4a**, and for imine **3b** no isomerization reaction occurred with such a catalyst. In order to improve the enantioselectivity of the amino alcohol catalysts, different *N*-protecting groups in these catalyst have to be considered.

6.2.4 Solvent variation

The solvent dependence on the enantioselectivity of the imine isomerization catalyzed by chiral potassium alkoxides derived from **24a** and **28a** was investigated. Comparison of the inducing ability of the catalysts using different solvents under otherwise similar reaction conditions showed that in toluene higher enantioselectivities were obtained than in THF (Tables 6.2, 6.3).

Table 6.5 Asymmetric imine isomerization of imine **4a** (R_1 = Ph) using chiral potassium alcoholates derived from **24a** and **28a** in different solvents

Entry	Reaction Conditions[a]			K_{eq}	TO number[d]	$t_{1/2}$ min[b]	e.e.$_{max}$ (%)[c] (Config)[c]
	Base	Solvent	Temp,°C				
1	**24a**	THF	66	2.00	58.9	1.6	1 (R)
2	**24a**	toluene	20	2.19	13.3	7.2	14 (R)
3	**28a**	toluene	20	2.03	14.2	6	34 (R)
4	**28a**[f]	toluene/ CH_2Cl_2[e]	24	--	--	390	10 (S)
5	**28a**	toluene/ THF[e]	24	2.08	2.2	43	5(R)
6	**28a**	toluene/ hexane[e]	24	2.08	7.9	11.9	27 (R)

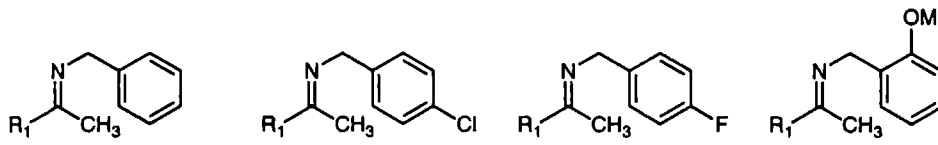
a) Concentration of potassium salt of catalysts **24a** and **28a** is 30 mol % and the imine concentration is 0.1 mmol/mL. b) The parameter $t_{1/2}$ is the reaction time for 50% conversion of the starting material; The method of calculation is described in the appendix in chapter 5. c) E.e. of **3b** determined by HPLC (Daicel Chiralpak AD) (eluent: hexane / 2-propanol = 99:1, v/v). d) TO-number = turnover number and is defined as mol product / mol catalyst / hour at t = 0. e) Toluene : co-solvent = 9:1, v/v). f) Equilibrium is not reached.

The highest e.e.'s in the isomerization of imine **4a** (34%, entries 15, Table 6.3) were observed for the potassium alcoholate derived from **28a** in toluene (Figure 6.4). In an attempt to increase the enantioselectivity of the imine isomerization reaction catalyzed by **28a**, dichloromethane, THF and hexane were added as co-solvents (10%) during the isomerization of imine **4a** in toluene. The addition of 10% hexane had a slight effect on the rate and the enantioselectivity of the reaction. However, when dichloromethane was added a reversal of enantioselectivity leading to the formation of (S)-imines in stead of (R)-imines was observed. This solvent effect can not be explained by a simple increase or decrease of the polarity or polarizability of the solvent mixture. The isomerization of imine **4a** into **6a** did not reach equilibrium and the presence of dichloromethane gave rise to side reactions. Under the basic reaction conditions used, carbenes and other highly reactive intermediates may be formed from dichloromethane which may be responsible for the decrease in the imine isomerization reaction rate due to catalyst and imine substrate degradation.

When THF was added as a co-solvent (10%) the enantioselectivity decreased considerably. These low enantioselectivities were also observed when the reaction of imine **4a** was performed in pure THF. The difference of the enantioselectivity in THF as compared to toluene is attributable to the difference in polarity of these solvents. The intermediate aza-allyl anions will be better solvated by THF than by toluene. Intimate ion-pairs, consisting of a chiral alkoxide base and an aza-allyl anions will be more stable in toluene than in THF which may be responsible for a higher enantioselectivity in the isomerization reaction. The decrease of the reaction rate in toluene in comparison with THF is due to a decrease in the activation energy (E_a) through a better stabilization of the aza-allyl anionic intermediate in the polar solvent THF than in the apolar solvent toluene.

6.2.5 Variation of the imine substrate

The enantioselectivities in the imine isomerization of the substituted imines **4a**, **4b**, **4e** and **4f** using chiral alkoxides derived from **9a**, **11** and **12a**, respectively, were investigated (Figure 6.9). The results are collected in Table 6.6.



4a **4b** **4e** **4f**

R_1 = Ph

Figure 6.9

When ephedrine (**9a**) and cinchonine (**12a**) were used as catalysts in the asymmetric isomerization of the *p*-F imine substrate **4e**, low enantioselectivities were observed. The enantioselectivities for the substrates **4a** and **4b** using quinine (**11**) and ephedrine (**9a**) are similar to those of imine **4e**. Apparently, the influence of the *p*-substituent on the enantioselectivity in the isomerization of the model imines **4a-e** is rather low.

Table 6.6 Asymmetric imine isomerization of imines **4a**, **4b**, **4e** and **4f** (R_1 = Ph) using chiral potassium alcoholates derived from **9a-12a**.

Entry	X	Reaction Conditions[a]			K_{eq}	TO number[d]	$t_{1/2}$ min[b]	e.e.$_{max}$ (%)[c] (Config)[c]
		Base	Solvent	Temp,°C				
1	*p*-F	**9a**	toluene	22	2.20	6.3	18	4 (R)
2	*p*-F	**9a**[e]	toluene	22	2.23	4.2	21	3 (S)
3	*p*-F	**12a**	toluene	22	2.21	1.0	95	5 (R)
4	*p*-Cl	**11**	toluene	22	1.53	1.5	51	9 (S)
5	*p*-H	**9a**	toluene	22	2.08	3.8	24.6	5 (R)
6	*p*-H	**9b**	toluene	22	2.12	23.4	4.0	6 (R)
7	*p*-H	**11**	toluene	22	2.15	1.7	55	11 (S)
8	*o*-OMe	**11**[f,g]	toluene	22	0.67	0.22	242	9 (S)

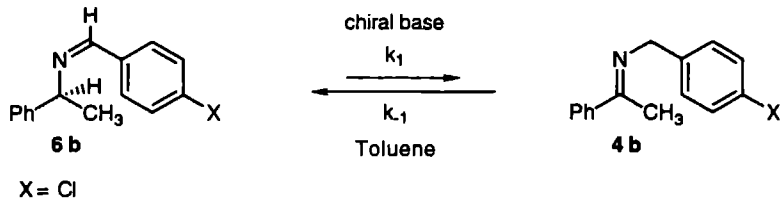
a) Concentration of potassium salt of catalysts **9a-12a** is 30 mol % and the imine concentration is 0.2 mmol/mL. b) The parameter $t_{1/2}$ is the reaction time for 50% conversion of the starting material; The method of calculation is described in the appendix in chapter 5. c) E.e. of product imine determined by HPLC (Daicel Chiralpak AD) (eluent: hexane / 2-propanol = 99:1, v/v). d) TO-number = turnover number and is defined as mol product / mol catalyst / hour at t = 0. e) (+)-Ephedrine was used. f) [Catalyst] = 60 mol %. g) [imine] = 0.1 mmol/mL.

In an attempt to improve the internal complexation of the aza-allyl anion intermediate with the potassium ion and the chiral alkoxide catalyst, an *ortho*-methoxy substituted imine **4f** was proposed as substrate. However, the enantioselectivity and the reaction rate of the asymmetric

isomerization of **4f** was disappointingly low. Moreover, the equilibrium of this imine substrate lies at the side of the starting material (**4f**:**6f**=60:40, K_{eq} = 0.67) and therefore, this model imine **4f** was not considered for further experiments.

6.2.6 Racemization experiments

The reaction conditions used for the isomerization of imine **4b** into product imine **6b** were also applied for the reverse imine isomerization reaction starting from enantiopure imine **6b** using quinine (**11**) as chiral base (Scheme 6.4). During these experiments the reaction constants (k_1 and k_{-1}) as well as the racemization constant (k_{rac}) of the starting imine **6b** (X=Cl) were obtained using GLC and HPLC techniques.



Scheme 6.4

The kinetic data for the isomerization reaction of model imine **6b** are collected in Table 6.7 and are compared with those of the isomerization of **4b** into **6b**. The determination of k_{rac} was performed using linear plots of ln[e.e(%)] versus time (see appendix chapter 5, equation A.27).

The data in Table 6.7 reveal that in both the forward (**4b=>6b**) and reverse (**6b=>4b**) imine isomerization experiments the equilibrium constants (K_{eq}) and the reaction constants (k_1 and k_{-1}) have almost similar values. The reaction constant k_1 (entry 2) for the reaction **4b=>6b** has to be compared with k_{-1} (entry 1) of the reaction **6b=>4b** and vice versa. For the isomerization of the imine systems **4b<=>6b** the experimental error is 2.5 %. This inaccuracy is within the range of the average experimental errors for the imine isomerization experiments described in section 5.2.4 (error ca. 5%).

For model imine **6b** the racemization constant (k_{rac}) was determined to be $2.5*10^{-3}$ min^{-1} and is smaller than the rate constant k_1 for **6b=>4b** ($5.78*10^{-3}$ min^{-1}) and the ratio of k_1/k_{rac} amounts to 2.3. This is in agreement with the results described in chapter 5 (see also the discussion in section 5.2.4).

Table 6.7 Imine isomerization and racemization kinetics of model imine **4b** and **6b** using quinine (**11**) as the catalyst

Entry (imine)	Temp. °C (K)	K_{eq} ($1/K_{eq}$)	k_{rac} (10^{-3} min^{-1})	k_1 (10^{-3} min^{-1})	k_{-1} (10^{-3} min^{-1})	k (10^{-3} min^{-1})
1 (**6b**)	22 (295)	0.688 (1.45)	2.5	5.78	8.32	14.1
2 (**4b**)	22 (295)	1.53	--	7.72	5.88	13.6

a) Concentration of the potassium salt of catalyst **11** is 30 mol % and the imine concentration is 0.2 mmol/mL.

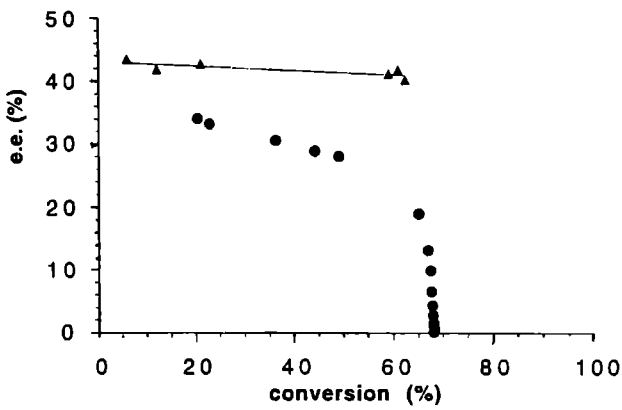
The enantioselectivity of the isomerization of chiral imine **6b** may be attributed to the intermediacy of a complex consisting of an intimate ion-pair[18] of an aza-allyl anion, a potassium ion (K^+), a chiral alkoxide molecule and one or more additional chiral imines **6b**. During the isomerization and the racemization of the aza-allyl anion, an intermolecular chirality transfer by the excess of chiral imine molecules **6b** and the chiral base in the complex may occur. The

enantioselectivity during the proton transfer for the isomerization of imine **6b** was calculated from k_1/k_{rac} and amounts to 23%

6.2.7 Comparison of the behavior of imines 3b and 4a

Comparison of the imine isomerization reaction of imines **3b**, derived from benzylacetone and *p*-chlorobenzylamine, and **4a**, derived from acetophenone and benzylamine, using the same solvent and chiral amino alcoholate catalyst **24a**, learns that the isomerization reaction of imine **4a** is much faster than that of imine **3b** The reason for this slower isomerization reaction of **3b** in comparison with **4a** is due to a higher activation energy (E_a) and a higher free energy of activation ($\Delta G^{\#}$) for the isomerization imine **3b** as compared to imine **4a** (see chapter 5) Furthermore, it is expected that the aza-allyl anion intermediate derived from **4a** is more stable than the corresponding intermediate derived from imine **3b**. When the reaction of imine **3b** was performed in toluene, it was even necessary to heat the reaction mixture to 105°C, because at lower temperatures only low conversions of **3b** into **5b** occurred The isomerization reaction of imine **3b** only reached equilibrium, when chiral alcohols **15-17**, prolinol derivative (**31**), quinine (**11**) and quinidine (**12b**) were used For all other catalysts equilibrium was never reached Another important difference in behavior of imine **4a** as compared to **3b** is that during the isomerization of imine **3b** almost no racemization of the imine product **5b** occurred (Figure 6 3)

Figure 6.9 Enantiomeric excess versus conversion during the asymmetric isomerization of imines **3b** and **4a** with chiral potassium alcoholates derived from **24a** and **28a** as catalysts



● E e (%) = enantiomeric excess of **6a** measured by HPLC and ▲ e e (%) = enantiomeric excess of **5b** measured by HPLC

For the asymmetric isomerization of imine **4a** equilibrium was reached in almost all cases The initially obtained enantioselectivities were also the maximum values, because during the reversible imine isomerization process racemization of the product **6a** took place (Figure 6 4) These differences in behavior for the racemization and the isomerization of imines **3b** and **4a** can be explained when catalyst degradation during the isomerization process of imine **3b** takes place, which does not occur in for **4a** The isomerization reactions of imine **3b** were performed in toluene at 105°C and in THF at 66°C Under these vigorous reaction conditions the chiral potassium alkoxides prepared from the amino alcohols are rather unstable Therefore, the first order reaction constants of the isomerization of imine **3b** could not be determined and only $t_{1/2}$-values and turnover numbers (TO-number) are shown in Table 6 2.

The differences in the isomerization of imines **3b** and **4a** can be visualized by plotting the enantiomeric excess versus conversion. For imine **3b** a linear correlation is found, whereas for **4a** a curve starting at the maximum enantioselectivity (e.e_{max}) and ending at an e.e.-value of zero is obtained From the curve of **4a** it is clear that at low conversions the racemization is also low. The closer the equilibrium is reached the more important the racemization process.

Additional evidence for the occurrence of catalyst degradation during the isomerization of **3b** was obtained from the asymmetric isomerization of imine **4a** using (-)-*N*-benzyl-*N*-methylephedrinium bromide (**10**) Under the applied basic reaction conditions this quarternary ammonium salt is unstable (section 6 2.3). It is known that under basic conditions quarternary ammonium alkoxides give intramolecular elimination reactions with relative ease.[19] For **10** an intramolecular epoxide ring closure reaction to give dimethylbenzylamine and 1-phenyl-2-methyl oxirane was observed and this degradation reaction could be monitored by GC/MS The quarternary ammonium compound **10** had been completely converted into these reaction products within 2h.

However, it was possible to partially isomerize imine **4a** using alkoxide catalyst **10** despite the degradation of the catalyst during the isomerization reaction. The reaction did not reach equilibrium and after some time no isomerization took place any longer During this process the enantioselectivity of the product imine **6a** remained almost constant and no racemization occurred, as was also observed for many isomerization reactions of imine **3b**

When isomerization reactions of imine **4a** were performed in THF at room temperature a fast reaction took place whereby no asymmetric induction in the product imine was observed. Changing from THF to toluene using the same chiral alcoholate bases (**9-34**), slowed down the imine isomerization reaction, as was also observed for imine **3b**, and in all cases the reaction proceeded in an asymmetric fashion (e.e. = 2-34%, Table 6 3).

The chiral potassium alcoholate catalysts **9-34** were effective in catalyzing the transformation of **3b** into **5b** and **4a** into **5a**. The chiral potassium alcoholates derived from **15-17** and **32-33** gave isomerization reactions for imines **3b** and **4a** in THF and toluene, but the e.e 's were very low (0-3%) (Tables 6.2 and 6.3). These chiral alcohols (**15-17** and **32-33**) are clearly not the catalysts of choice in the asymmetric imine isomerization reaction

When Li^+ and Na^+ were used instead of K^+ counterions no imine isomerization reaction occurred when imine **3b** was used. For imine **4a** only chiral alcohol and aminoalcohol alkoxides with a K^+-ion were applied. Highering the concentration of the chiral catalyst did not improve in the enantioselectivity, but the rate of the imine isomerization reaction is faster (Table 6.2, entries 1-4 and 11-13)

6.2.8 Synthesis of chiral amines 7b and 8a

The crude product mixtures of imines **3b** and **5b**, and **4a** and **6a**, respectively, were hydrolyzed after equilibrium was reached using 2M sulfuric acid, whereby the product amines **7b** and **8a** along with the *p*-substituted benzylamines were isolated in good yields (85-95%) using acid-base extraction The crude product mixtures were not purified but as such analyzed by NMR, IR and GC/MS. After hydrolysis the e.e. of the crude amine **7b** was checked by GLC (Mosher acid chloride derivative) and HPLC (benzaldehyde derived imine derivative) using a chiral column (Chiralpak AD). The e.e. of amine **7b**, obtained after hydrolysis of **5b**, was identical to that of imine **5b** before hydrolysis (Figure 6.3), implying that no racemization had occurred during the hydrolysis and work-up procedure For amine **8a** the same procedure as described for **7b** was followed, yielding an amine product **8a** that had undergone isomerization under the conditions of the imine isomerization reaction (Figure 6 4).

6.3 Conclusion

This work shows that chiral aminoalcohols, especially chiral *N*-trityl aziridine carbinols **22-28**, are sofar the best catalysts for the asymmetric catalytic isomerization of prochiral imines. Chiral alcohols give low inductions in this asymmetric process. It is worth noting that in these new catalysts ligands with *N*-trityl groups give good results. The chiral catalysts quinine (**11**), quinidine (**12b**), and ephedrine (**9a**) give relatively low e.e.'s as compared to the *N*-trityl-aziridine-2-carbinols **22-28**.

Induction of the asymmetric imine isomerization reaction is not dependent on the catalyst concentration. Kinetic studies have shown that the e.e.'s decrease with the conversion for imines derived from acetophenone and benzylamine (imine **4a**) and this is attributable to the racemization of the product imine under the basic reaction conditions. However, the racemization reaction constant (k_{rac}) is smaller than the reaction constant for the reverse reaction (k_{-1}). For the imine derived from benzylacetone and p-Cl-benzylamine (imine **3b**) almost no racemization occurred during the isomerization reaction which is most certainly due to catalyst degradation during the vigorous reaction conditions. This is confirmed by the observation that equilibrium is not reached because of the deactivation of the chiral catalyst.

A general method for the catalytic asymmetric synthesis of chiral amines via a [1,3]-proton transfer reaction was developed.[6] The method described in this chapter using chiral potassium alkoxide bases is more generally applicable in the asymmetric [1,3]-proton shift reactions than that reported recently by Soloshonok (see section 6.1).

6.4 Experimental section

General Methods All reactions were conducted under an atmosphere of argon, using standard Schlenk techniques. Optical rotations were determined with a Perkin-Elmer automatic polarimeter, model 241 MC using 1% solutions at 20°C in the solvents indicated Melting points were determined using a Reichert thermopan microscope equipped with crossed polarizers, and are uncorrected. GLC was conducted with a Hewlett-Packard HP5890A and HP 5790A gas chromatograph, using a capillary column (25m) of HP-1 and PAS-1701, a temperature program from 190-250°C at 10°C/min, followed by 10 min at 250°C (isothermal), and nitrogen at 2 ml/min (0 5 atm) as the carrier gas. The instruments were connected to a HP 3396 or HP 3390 calculating integrator. The enantiomeric purity of imines **5a-f**, **6a-f** and the aziridine-2-carbinols **22-28** was determined by HPLC[15] using chiral columns with *n*-hexane/2-propanol (ratio as indicated) as the eluent. The chromatographic system consisted of a Pharmacia LKB (Sweden) model 2150 HPLC pump, a LKB model 2152 HPLC controller and a Rheodyne injector The injection loop had a 20-µl capacity. The columns used were a Daicel Chiralpak AD (250*4 6 mm I.D., 10 µm) and a Chiralcel OD (250*4 6 mm I.D., 10 µm) from J.T Baker (Deventer, The Netherlands) The flow rate was 0 60 ml/min or 0.75 ml/min and the columns were operated at ambient temperature. The column effluent was monitored with an LKB model 2138 uvicord S absorbance detector at 254 nm. UV spectra of Schiff base derivatives were recorded with a Perkin-Elmer lamba 5 UV/Vis spectrofotometer ^{1}H- and ^{13}C-NMR were performed on a Bruker AC 100 (100 MHz, FT) spectrometer using solutions in $CDCl_3$ (internal standard· Me_4Si) IR spectra were determined on a Perkin Elmer 298 spectrophotometer FT IR spectra were determined on a Perkin Elmer 1720-X Infra-red Fourier Transform spectrometer Elemental analyses were performed on a Carlo Erba Instruments CHNS-O EA 1108 element analyzer. Electron impact (EI) and chemical ionization (CI) mass spectra, induced with methane gas at 200°C and emission current 0.5 mA, were determined on a VG 7070E spectrometer. For GC-mass spectrometry, a Varian Saturn benchtop GC-MS apparatus with a Varian 8100 autosampler was used. MS analysis was performed using electron impact (EI).

Chemicals Diethyl ether was pre-dried over calcium chloride, then distilled from calcium hydride. Tetrahedrofuran was distilled from lithium aluminum hydride. Benzene and absolute ethanol (both Merck p a quality) were used without further purification. All other solvents were either P A. or "reinst" quality (±)- and (R)-(+)-4-phenyl-2-aminobutane were a gift of DSM-Andeno (Venlo, the Netherlands). All other reagents are commercially available and were used as received. Unless otherwise stated, yields refer to isolated yields of products of greater than 95% purity as estimated by capillary GC and /or ^{1}H NMR spectroscopy.

Synthesis of model-imines 3a-f, 4a-f, 5a-f and 6a-f

The synthesis of imines **3a-f**, **4a-f**, **5a-f** and **6a-f** was performed using the procedures A, B, C and D as described in chapter 5

Synthesis of new chiral catalysts

The syntheses of the *N*-trityl-aziridine-2-carboxylic esters derived from L-serine and L-threonine, and that of *N*-trityl-aziridine-carbinols **24a-b** and **28a-b** derived therefrom (R = Ph) were described in chapters 3 and 4 *N*-trityl-aziridine-carbinol **22a** (R = Me) was prepared using a Grignard reagent, for *N*-trityl-aziridine-carbinols **23a-27a** R-Li reagents were used The synthesis of aziridin-2-yl-diphenylmethanol (**30a**) was described in chapter 4 (of compound **1a**)

(+)-(2S)-2-(1-Trityl-aziridin-2-yl)-propane-2-ol (22a)

To a stirred suspension of magnesium turnings (6 45 g, 265 mmol, 3 5 equiv) in ether (125 ml) methyl iodide (16 0 ml, 257 mmol, 3 5 equiv) in ether (25 mL) was gradually added The magnesium was activated by magnetic stirring overnight under an argon atmosphere [20] After heating the Grignard reagent for 1 5 h compound **20a** (R_1=H) (25 0 g, 72 6 mmol) in THF (100 mL) was added dropwise over a period of 20 min The reaction was monitored with capillary GLC and TLC (CH_2Cl_2) After 2 h the reaction was quenched with a saturated $(NH_4)_2SO_4$ solution (60 mL) and sodium sulphite (15 mL) to reduce the excess iodide present in the reaction mixture Then the organic solvents were removed The residue was extracted with ether (3x 50 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated Crude yield 92% (23 0 g, 67 0 mmol) of a yellow crystalline compound The crude product was purified by flash column chromatography (hexane/ethyl acetate 9 1) whereby NEt_3 (1 mL/L) was added to the eluent to prevent detritylation of the product during the purification step Yield 20 0 g (80%) of a white crystalline compound (**22a**) Purity 98 5% according to capillary GLC m p 86-87 5°C $[\alpha]^{20}_D$ = +28 2° (c=1, $CHCl_3$) Calc for $C_{24}H_{25}NO$ (343 47) C 83 93, H 7 34, N 4 08 %, found C 83 27, H 7 30, N 4 05 % MS (EI) m/e 266 (M-$C_6H_5^+$, 2 5%), 243 (Trt^+, 100%), 165 (Trt-Ph^+, 41 7%), 91 ($C_7H_7^+$, 8 0%), 77 ($C_6H_5^+$, 5 3%) ^{1}H NMR (100 MHz in $CDCl_3$), δ = 7 54-7 21 (m, 15H, aromatic H, Trt), 3 07 (s, 1H, OH), 1 87 (d, 1H, J = 3 2Hz, αCH, Azy), 1 36 (dd, 1H, J = 6 2 and 3 2Hz, βCH, Azy), 1 16 and 1 07 (s, 2x 3H, 2x Me), 1 13 (d, 1H, J = 6 2 Hz, βCH, Azy) ppm ^{13}C NMR (25 2 MHz in $CDCl_3$), δ = 144 2-126 8 (aromatic C), 73 7 (Ph_3CN), 67 4 (COH alcohol), 42 3 (αCH, Azy), 29 4 and 28 4 (2x Me), 23 4 (βCH, Azy) ppm IR (KBr) υ = 3500-3300 (OH), 3100-3000, 1600 (aromatic), 3000-2900 (alkyl) cm^{-1}

(-)-(2R)-2-(1-Trityl-aziridin-2-yl)-propane-2-ol (22b)

Using the same procedure as described for **22a**, compound **20b** (R_1 =H) (6 9 g, 20 1 mmol) was converted into **22b** using a Grignard reaction The Grignard reagent was prepared by using magnesium turnings (1 76 g, 72 4 mmol) and methyl iodide (4 47 mL, 71 8 mmol) in ether (20 mL) Yield 92% (6 33 g, 18 4 mmol) of a yellow oily compound The crude product was purified by flash column chromatography (petroleum ether/ethyl acetate 9 1) whereby NEt_3 (1 mL/L) was added to the eluent to prevent detritylation of the product during purification Yield 4 49 g (65%) of a white crystalline compound (**22b**) Purity 98 5% according to capillary GLC m p 85 5-87 5°C $[\alpha]^{20}_D$ -32 2° (c=1, $CHCl_3$) Calc for $C_{24}H_{25}NO$ (343 47) C 83 93, H 7 34, N 4 08 %, found C 83 24, H 7 31, N 4 04 % MS (EI) m/e 266 (M-$C_6H_5^+$, 2 4%), 243 (Trt^+, 77 9%), 165 (Trt-Ph^+, 100%), 91 ($C_7H_7^+$ 13 7%), 77 ($C_6H_5^+$, 10 6%) ^{1}H NMR (100 MHz in $CDCl_3$), δ = 7 54-7 21 (m, 15H, aromatic H, Trt), 3 06 (s, 1H, OH), 1 87 (d, 1H, J = 3 2Hz, αCH, Azy), 1 36 (dd, 1H, J = 6 4 and 3 2Hz, βCH, Azy), 1 16 and 1 07 (s, 2x 3H, 2x Me), 1 09 (d, 1H, J = 6 4Hz, βCH, Azy) ppm ^{13}C NMR (25 2 MHz in $CDCl_3$), δ = 144 1-126 8 (aromatic C), 73 7 (Ph_3CN), 67 3 (COH alcohol), 42 2 (αCH, Azy), 29 4 and 29 35 (2x Me), 26 4 (βCH, Azy) ppm IR (KBr) υ = 3500-3300 (OH), 3100-3000, 1600 (aromatic), 3000-2900 (alkyl) cm^{-1}

(-)-(2S)-5-(1-trityl-aziridin-2-yl)-nonan-5-ol (23a)

n-Butyllithium (11 2 mmol, 7 0 ml, 1 6 M solution in *n*-hexane) was dissolved in THF (10 ml) at 0°C with stirring and this solution was cooled to -78°C Compound **20a** (1 70 g, 5 0 mmol) dissolved in THF (15 ml) was added dropwise over a period of 15 min The reaction was monitored with TLC (CH_2Cl_2) After 75 min the mixture was warmed up to room temperature and the reaction was quenched with saturated $(NH_4)_2SO_4$ solution (20 ml) and ether (20 ml) was added The layers were separated and the aqueous layer was extracted twice with ether (25 ml) The combined organic layers were dried over $MgSO_4$, filtered over kiesel gel and the solvents were evaporated *in vacuo* Crude yield 94% (2 00 g, 4 7 mmol) of a thick foaming brown-yellow oil The crude product was purified by flash column chromatography (hexane/ethyl acetate 20 1) Yield 56% (1 18 g, 2 8 mmol) of a viscous colorless oil (**23a**) $[\alpha]^{20}_D$ -16 2° (c=1, $CHCl_3$) MS (EI) m/e 427 (M^+, 0 95%), 243 (Trt^+, 100%), 165 (Trt-Ph^+, 54 7%) ^{1}H-NMR (100 MHz in $CDCl_3$) δ = 7 43-7 07 (m, 15 H, Trityl), 2 97 (s, 1H, OH), 1 86 (d, 1H, J= 1Hz, βCH, Azy), 1 36-0 64 (m, 20H, αCH and βCH and alkyl) ppm ^{13}C-NMR (25 2 MHz in $CDCl_3$) δ =

144 2-126 9 (aromatic C), 74 1 (Ph_3CN), 70 6 (COH alcohol), 40 5-14 1 (alkyl C) ppm IR (CCl_4) υ= 3550-3350 (OH), 3080-3020, 1600 (aromatic), 2960-2940, 2880 (alkyl) cm^{-1}

(-)-(2S)-Bis-(4-methoxy-phenyl)-(1-trityl-aziridin-2-yl)-methanol (25a)

n-Butyllithium (11 1 mmol, 6 5 ml, 1 6 M solution in *n*-hexane) was dissolved in THF (10 ml) at 0°C and that solution was cooled to -78°C 4-Methoxybromobenzene (2 24 g, 10 2 mmol) dissolved in THF (20 ml) was added dropwise over a period of 20 min After addition, the solution was stirred for 20 min and then the temperature was raised to -65°C Compound **20a** dissolved in THF (15 ml) was then added dropwise over a period of 15 min to the solution of *p*-methoxyphenyllithium After addition the solution was stirred for 1 5 h at -60°C and then warmed up to room temperature The reaction was quenched with 25 ml saturated $(NH_4)_2SO_4$ solution, the layers were separated and the aqueous layer was extracted twice with ether (25ml) The combined organic layers were dried over $MgSO_4$ and filtered over kiesel gel The organic solvents were removed *in vacuo* Crude yield 99% (2 64 g, 5 0 mmol) of a light-yellow foam The crude product was purified by flash column chromatography (hexane/ethyl acetate 4 1) Yield 68% (1 80 g, 3 4 mmol) of a white crystalline compound (**25a**) m p 65-68°C $[\alpha]^{20}_D$ -107° (c=1, $CHCl_3$) MS (EI) m/e 527 (M^+, 0 1%), 285 (M^+-Trt, 17%), 243 (Trt^+, 100%), 165 ($C(C_6H_5)_2^+$, 37 5%), 91 ($C_6H_5CH_2^+$, 6 4%), 77 ($C_6H_5^+$, 8 3%) ^{1}H-NMR (100 MHz in $CDCl_3$) δ= 7 37- 6 64 (m, 25H aromatic H Trt, Phenyl), 4 23 (s, 1H, OH), 3 75 and 3 70 (2s, OCH_3), 2 25 (dd, 1H, αCH, Azy), 2 03 (d, 1H, J=3Hz, βCH, Azy), 1 97 (d, 1H, βCH, Azy) ppm ^{13}C-NMR (25 2 MHz in $CDCl_3$) δ = 158 3-113 1 (aromatic C), 74 0 and 73 6 (Ph_3CN and COH), 55 2 and 55 1 (OCH_3), 41 7 (αCH, Azy), 23 9 (βCH, Azy) ppm IR (CCl_4) υ= 3500-3300 (OH), 3100-3000, 1600 (aromatic), 2960-2900 (alkyl), 1140 (OCH_3) cm^{-1}

(+)-(2S)-1-trityl-aziridin-2-yl-diphenylmethanol (24a)

Using the same procedure as described for **23a**, compound **20a** (0 85 g, 2 5 mmol) was converted into **24a** using bromobenzene (0 82 g, 5 2 mmol) and *n*-butyllithium (3 3 ml 1 6 M solution in *n* hexane, 5 3 mmol) Crude yield 90% (1 16 g, 2 25 mmol) of a viscous grey-white foam The crude product was purified by flash column chromatography (hexane/ethyl acetate 6 1) Yield 55% (0 65 g, 1 40 mmol) of a white foam (**24a**) $[\alpha]^{20}_D$= +79 5° (c=1, $CHCl_3$) Calc for $C_{34}H_{29}NO$ (467 6) C 87 33, H 6 25, N 3 00 %, found C 87 02, H 6 38, N 3 07 % MS (EI) m/e 390 (M^+-C_6H_5, 2 1%), 243 (Trt^+, 100%), 183 (($(C_6H_5)_2$-OH^+, 48%), 165 ($C(C_6H_5)_2^+$ 61%), 105 ($C_6H_5CO^+$, 32 5%), 91 ($C_6H_5CH_2^+$, 11 7%), 77 ($C_6H_5^+$, 24%) ^{1}H-NMR (100 MHz in $CDCl_3$) δ = 7 40 7 02 (m, 25H, aromatic H, Trt, Phenyl), 4 35 (s, 1H, OH), 2 30 (dd, 1H J= 6 3 and 3 3 Hz, α CH, Azy), 1 99 (d, 1H, J= 3 5 Hz, βCH, Azy), 1 24 (d, 1H, J=6 3 Hz, βCH, Azy) ppm ^{13}C-NMR (25 2 MHz in $CDCl_3$) δ = 146 9-125 7 (aromatic C), 74 0 and 73 9 (Ph_3CN and COH alcohol), 41 4 (αCH, Azy), 23 8 (βCH, Azy) ppm IR (CCl_4) υ= 3500-3300 (OH), 3100-3000, 1600 (aromatic), 2980 (alkyl) cm ^{1}

(-)-(2S)-Bis-naphtalen-2-yl-(1-trityl-aziridin-2-yl)-methanol (26a)

Using the same procedure as described for **23a**, compound **20a** (1 70 g, 5 0 mmol) was converted into **26a** using 2-bromonaphthalene (2 30 g, 11 0 mmol) and *n*-butyllithium (7 0 ml, 1 6 M, solution in *n*-hexane, 11 2 mmol) Crude yield 99% (2 80 g, 4 95 mmol) of a viscous grey-white foam The crude product was purified by flash column chromatography (hexane/ethyl acetate 10 1) Yield 50% (1 40 g, 2 5 mmol) of a white crystalline compound (**26a**) $[\alpha]^{20}_D$= -128 6° (c=1, $CHCl_3$) Calc for $C_{42}H_{33}NO$ (567 73) C 88 86, H 5 86, N 2 47 %, found C 88 25, H 6 51, N 2 33 % MS (EI) m/e 567 (M^+, 0 2%), 324 (M^+-Trt, 0 5%), 308 (M^+-Trt-O, 1 2%), 243 (Trt^+, 100%), 165 ($C(C_6H_5)_2^+$, 56 3%), 155 ($C_8H_{10}C{=}O^+$, 32 7%), 127 ($C_8H_{10}^+$, 15 5%), 91 ($C_6H_5CH_2^+$) ^{1}H-NMR (100 MHz in $CDCl_3$) δ = 8 00-7 05 (m, 25 H, aromatic H, Trt, Phenyl), 4 60 (s, 1H, OH), 2 55 (dd, 1H, J= 3 and 6Hz, αCH, Azy), 2 18 (d, 1H, J= 6Hz, βCH, Azy), 1 39 (d, 1H, J= 6Hz, βCH, Azy) ppm ^{13}C NMR (25 2 MHz in $CDCl_3$) δ = 144 0-124 4 (aromatic C), 74 6 and 74 2 (Ph_3CN and COH), 41 3 (αCH, Azy), 24 1 (βCH) ppm IR (CCl_4) υ= 3500-3200 (OH), 3100-3000, 1600 (aromatic), 2980 (alkyl) cm^{-1}

(-)-(2S)-Bis-phenanthren-9-yl-(1-trityl-aziridin-2-yl)-methanol (27a)

Using the same procedure as described for **23a**, compound **20a** (1 70 g, 5 0 mmol) was converted into **27a** using 9-bromophenantrene (2 57 g, 10 0 mmol) and *n*-butyllithium (6 5 ml 1 6 M, solution in *n*-hexane, 10 4 mmol) for the bromide/lithium exchange Crude yield 99% (3 30 g, 4 95 mmol) of a light-yellow crystalline compound The crude product was purified by flash column chromatography (hexane/ethylacetate 12 1) Yield 50% (1 65 g, 2 5 mmol) of a white solid (**27a**) Crystallization from MeOH/NEt3 (50mL/15 drops) afforded 1 17 g (35%) of a white solid compound **27a** m p 189-192°C $[\alpha]^{20}_D$ -102° (c=1, $CHCl_3$) MS (EI) m/e 667 (M^+, 0 1%), 424 (M^+-Trt, 1 1%), 408 (M^+-Trt-O), 243 (Trt^+, 51 5%), 205 ($C_{14}H_9C{=}O^+$, 100%), 177 ($C_{14}H_9^+$, 38 6%), 165 ($C\phi_2CH_2^+$, 28%) ^{1}H-NMR (100 MHz in $CDCl_3$) δ = 8 46-6 67 (m, 33H, aromatic H), 5 14 (s, 1H, OH), 2 74

(m, 1H, αCH, Azy), 2,26 (d, 1H, J=0 5Hz, βCH, Azy), 1 42 (d, 1H, J=1Hz, βCH, Azy) ppm ^{13}C-NMR (25 2 MHz in $CDCl_3$) δ = 143 6-122 2 (aromatic C), 78 0 and 74 9 (COH and Ph_3CN), 42 7 (αCH, Azy), 25 4 (βCH, Azy) ppm IR (CCl_4) υ= 3500-3200 (OH), 3100-3000, 1600 (aromatic), 2980-2850 (alkyl+aryl) cm^{-1}

(-)-(1R,2S)-N-trityl-ephedrine (29)

(-)-(1R, 2S)-ephedrine (**9a**) (1 00 g, 6 05 mmol) was dissolved in $CHCl_3$ (20 mL, ethanol free) at room temperature Triethylamine (1 75 mL, 12 1 mmol, 2 0 equiv) was added, followed by the gradual addition of trityl chloride (1 69 g, 6 05 mmol, 1 0 equiv) dissolved in $CHCl_3$ (10 mL) during a period of 15 min The reaction was monitored with TLC (petroleumether/ethyl acetate = 2 1) After 15 h the reaction mixture was concentrated, and dissolved in ether (15 mL) The precipitate (NEt_3 HCl) was filtered off and the crude reaction mixture was extracted with an aqueous citric acid solution (10%) (3x 10 mL) and a saturated $NaCO_3$ solution (3x 10 mL) The combined organic layers were dried ($MgSO_4$) and concentrated affording a white solid compound **29** Yield 92% (2 27 g) Purity >90% according to NMR, TLC 1 spot m p 115-120°C $[\alpha]^{20}_D$= -40 7° (c=1, $CHCl_3$) ^{1}H-NMR (100 MHz in $CDCl_3$) δ = 7 6-7 0 (m, 20H, aromatic H), 4 25 (d, 1H, J=9 2 Hz, $PhC_1\underline{H}OH$), 3 50 (m, 1H, $Me\underline{H}C_2N$-trityl), 2 9 (s, 1H, OH, broad), 2 16 (s, 3H, $NC\underline{H}_3$), 0 0 (d, 3H, J=6 2 Hz, $C_2C\underline{H}_3$) ppm IR (CCl_4) υ= 3610 (free-OH), 3100-3000, 1600 (aromatic), 2980-2820 (alkyl+aryl) cm^{-1}

(-)-(S)-2-(N-methylpyrrolidine-2-yl)-propane-2-ol (31)

( )-(S)-2-(N-methylpyrrolidine-2-yl)-propane-2-ol (**31**) was obtained following a literature procedure[21] from (S)-*N*-(benzyloxycarbonyl)proline methyl ester by a reaction with methylmagnesium iodide and subsequent reduction with $LiAlH_4$ Yield 65% (704 mg) Purity 97% according to GLC $[\alpha]^{20}_D$= -5 4° (c=1, $CHCl_3$) ^{1}H-NMR (100 MHz in $CDCl_3$) δ = 3 35-2 96 (m, 1H,), 2 61 (s, 1H, OH, broad), 2 50 (s, 3H, N-$C\underline{H}_3$), 2 46-2 30 (m, 2H), 1 82-1 67 (m, 4H), 1 20 (s, 3H, $C\underline{H}_3$), 1 12 (s, 3H, $C\underline{H}_3$) ppm IR (CCl_4) υ= 3610 (free-OH), 2980-2820 (alkyl) cm^{-1}

Catalysts **32-33** (*vide infra*) were prepared following a literature procedure from L-diethyl tartrate (DET) [22] 2,2–Dimethyl-1,3-dioxolan-4,5-dicarboxylic dimethyl ester was treated with methylmagnesium iodide and phenylmagnesium bromide, respectively

α,α,α',α'-tetramethyl-1,3-dioxolan-4,5-dimethanol (32)

Yield 94% (5 15 g) Purity 97% according to GLC $[\alpha]^{20}_D$ +7 4° (c=1, $CHCl_3$), m p 153-154°C ^{1}H-NMR (100 MHz in $CDCl_3$) δ = 4 24 (s, 2H, $C_1\underline{H}$-$C_2\underline{H}$), 3 72 (s, 1H, OH), 1 37 (s, 6H, 2*$C\underline{H}_3$ dioxolane), 1 31 (s, 6H, 2*$C\underline{H}_3$-carbinol), 1 26 (s, 6H, 2*$C\underline{H}_3$-carbinol) ppm ^{13}C-NMR (25 2 MHz in $CDCl_3$) δ = 107 5 (C-dioxolane), 82 6 (2*C-tartrate), 70 4 (2*C-carbinol), 29 1 (CH_3-carbinol), 27 2 (CH_3-dioxolane), 23 5 (CH_3-carbinol) ppm IR (CCl_4) υ= 3500-3200 (OH), 2980-2820 (alkyl) cm^{-1}

α,α,α',α'-tetraphenyl-1,3-dioxolan-4,5-dimethanol (33)

Yield 64% (8 24 g) $[\alpha]^{20}_D$ -68 2° (c=1 $CHCl_3$), m p 190-192°C ^{1}H-NMR (100 MHz in $CDCl_3$) δ = 7 52-7 16 (m, 20H, aromatic), 4 58 (s, 2H, $C_1\underline{H}$-$C_2\underline{H}$-tartrate), 4 02 (s, 1H, OH, broad), 1 01 (s, 6H, 2*$C\underline{H}_3$-dioxolane) ppm ^{13}C-NMR (25 2 MHz in $CDCl_3$) δ = 145 9-127 3 (C-aromatic), 109 6 (C-dioxolane), 80 9 (2*C-tartrate), 76 2 (2*C-carbinol), 27 2 (CH_3-dioxolane) ppm IR (CCl_4) υ= 3500-3200 (OH), 3100-3000, 1600 (aromatic), 2980-2820 (alkyl) cm^{-1}

(-)-(S)-(1-phenylethyl-azetidin-2-yl)-diphenyl methanol (34)

Catalyst **34** was prepared by a modified literature procedure[14] from γ-butyrolactone in 5 steps To a stirred suspension of magnesium turnings (1 3 g, 57 2 mmol, 4 2 equiv) in ether (15 ml) bromobenzene (8 6 g, 54 8 mmol) in ether (10 mL) was gradually added The magnesium was activated by magnetic stirring overnight under an argon atmosphere [20] After heating the Grignard reagent for 30 min methyl-1-[(S)-1-phenylethyl]-azetidine-2-carboxylate (3 0 g, 13 7 mmol) in ether (15 mL) was added dropwise over a period of 10 min The reaction was monitored by TLC After 1 h the reaction was quenched with a saturated NH_4Cl solution (50 mL) and ether (50 ml) was added The layers were separated and the aqueous layer was extracted three times with ether (50 ml) The combined organic layers were washed with a saturated $NaCO_3$ solution, dried over $MgSO_4$, filtered over silica gel and evaporated *in vacuo* Crude yield 98% (4 6 g) of a brown viscous oil **34** The crude product was purified by flash column chromatography (hexane/ethyl acetate 4 1) Yield 3 6 g (77%) of a white crystalline compound Crystallization from hexane afforded 2 6 g (55%) of **34**, m p 91-93°C, $[\alpha]^{20}_D$ = -14 0° (c=1, $CHCl_3$) Calc for $C_{24}H_{25}NO$ (343 47) C 83 93, H 7 34, N 4 08 %, found C 83 61, H 7 28, N 4 19 % ^{1}H NMR (100 MHz in $CDCl_3$), δ = 7 66-6 67 (m, 15H, aromatic H), 5 60 (s, 1H, OH, broad), 4 26 (t, 1H, J = 9 0 Hz, $C_2\underline{H}$-Azetidine), 3 30-2 83 (m, 3H, $C_4\underline{H}_2$-azetidine, H-phenylmethyl), 2 07-1 65 (m, 2H, $C_3\underline{H}_2$), 0 85 (d, 3H, J = 6 5Hz, CH_3) ppm ^{13}C NMR (25 2 MHz in $CDCl_3$), δ = 146 1-125 7 (aromatic C), 75 7 ($Ph_2\underline{C}OH$), 69 6 (C_2-azetidine), 61 2

(C-phenylmethyl), 45 0 (C_4-azetidine), 19 8 (CH_3), 19 6 (C_3-azetidine) ppm IR (KBr) υ = 3500-3300 (OH), 3100-3000, 1600 (aromatic), 3000-2900 (alkyl) cm^{-1}

General procedure for the isomerization of imines 3b and 4a using potassium alkoxides from chiral alcohols and amino alcohols.

Isomerization of imine 5b using 30 mol% 9-34 as the catalyst The reactions were run under an argon atmosphere in a flame dried 3-necked reaction flask Chiral catalysts **9-34** (0 3 mmol) were dissolved in toluene (2 0 mL) followed by the addition of a KH suspension in toluene (6 0 mL, 0 3 mmol) Hydrogen evolved immediately This solution was heated at 105°C for 1 h When THF was used as the solvent the reaction mixture was stirred at 66°C for 1 5 h Imine **3b** (1 0 mmol) was dissolved in toluene (2 0 mL) and then added to the chiral potassium alkoxide catalyst suspension in toluene at 105°C The isomerization reaction was monitored by GLC and HPLC Aliquots were taken from the reaction mixture using a syringe, which were immediately quenched with an aqueous NaOH(30-50%)/ether mixture These samples could be stored in the refrigerator for several years The monitoring of the reaction was continued until the starting material/product ratio had stabilized and equilibrium was reached Determination of the conversion of imine **3b** into imine **5b** was performed by GLC (HP-1 column 25m) The enantiomeric excess of imine **5b** was determined by HPLC-analysis using a Chiralpak AD column (flowrate 0 65 mL/min, eluent **5b** 2-propanol/*n*-hexane 1/99)

Isomerization of imine 6a using 30 mol% 9-34 as the catalyst The reactions were run under an argon atmosphere in a flame dried 3-necked reaction flask Chiral catalysts **9-34** (0 3 mmol) were dissolved in toluene (2 0 mL) followed by the addition of a KH suspension in toluene (6 0 mL, 0 3 mmol) Hydrogen evolved immediately This solution was heated at 70-80°C for 1 h, cooled to room temperature and left at ambient tempareture for 1 5 h Imine **4a** (1 0 mmol) in toluene (2 0 mL) was added to the chiral potassium alkoxide catalyst suspension at room temperature The isomerization reaction was monitored by GLC and HPLC Samples were taken from the reaction mixture using a syringe, and immediately quenched in an aqueous NaOH(30-50%)/ether mixture These imine samples could be stored in the refrigerator for several years The monitoring of the reaction was continued until the starting material/product ratio had stabilized and equilibrium was reached Determination of the conversion of imine **4a** into imine **6a** was performed by GLC (PAS-1701 or HP-1 column 25m) and HPLC The enantiomeric excess of imine **6a** was determined by HPLC-analysis, using a Chiralpak AD column (flowrate 0 65 mL/min, eluent **6a** 2 propanol/*n*-hexane 1/99)

Hydrolysis of imines 5a-f and 6a-f The crude reaction products were hydrolyzed using 2M H_2SO_4 in a mixture of THF and ether for 24h The reaction was monitored using GLC The amines **7a-f** and **8a-f** were separated from the aldehydes by acid-base extraction procedure and the combined organic layers were dried ($MgSO_4$) and concentrated The enantiopurity of the product amines **7a-f** and **8a-f** was determined using HPLC (Chiralpak AD) according to a procedure as described in chapter 7

6.5 References

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Chapter 7

High-performance Liquid Chromatography of Imine Isomers on Cellulose-based Chiral Stationary Phases

7.1 Introduction.

The importance of optical purity in connection with biological activity (chapter 1) has created a growing need for fast and accurate methods in the determination of enantiomeric purity The classical method for the determination of enantiopurity of chiral compounds is measurement of the specific optical rotation The optical rotation $[\alpha]^{t}_{\lambda}$ is obtained by using a polarimeter and the enantiopurity of a sample is determined by comparison of the measured value with the known optical rotation for an enantiopure compound

The reliability and the accuracy of this method of analysis was already questioned by Valentine and coworkers[1] in 1978 First of all, optical purity and enantiopurity are not always equivalent, as has been demonstrated in several cases [2] A second limitation is that many examples of incorrect optical rotations for compounds considered to be enantiopure have appeared in the literature Finally, the use of optical rotation for determination of enantiopurity may be uncertain, due to a contamination of the chiral product with an optically active impurity This may become really problematic if the impurities have a high rotation or a rotation of the opposite sign to that of the substrate being analyzed

Therefore, it is necessary to apply more accurate independent methods of analysis for the determination of enantiopurity of chiral compounds Progress has been made in the development of NMR methods[3] in the last decade and also new sensitive and accurate GLC[4] and HPLC[5] methods have been developed Gas chromatographic and high performance liquid chromatographic methods in particular, are more accurate than NMR methods, and therefore preferred for quality control in pharmaceutical and fine chemical applications The HPLC methods for chiral analysis are used increasingly, as a result of improvements in column lifetime and performance

On regular (achiral) stationary phases enantiomers cannot be separated, because they have the same chemical properties Therefore, chromatographic separation of enantiomers has to be accomplished using other methods The first method involves precolumn derivatization of the sample with a chiral reagent, giving diastereomers which can be separated on achiral columns [6] A second, more desirable and direct method, uses the formation of transient diastereomers via the interaction of enantiomers with a chiral selector present as a chiral mobile phase additive (CMPA) or as a chiral stationary phase (CSP)

The subject of HPLC in combination with chiral columns has been extensively reviewed over the years [7] Many chiral stationary phases (CSPs) have been described and a large number of them are commercially available at the moment Examples of types of CSPs are the chiral ligand exchange phases, the affinity phases, the cavity phases, the Pirkle type phases and the chiral helical polymer phases [8]

In the course of this study new chiral columns based on chiral helical polymers became

available on a commercial basis Helical polymer phases include cellulose derivatives, amylose derivatives and synthetic polymers such as poly(triphenylmethyl) methacrylate For example, a variety of cellulose derivatives and amylose derivatives adsorbed on macroporous silica are commercially available (Figure 7 1) [9]

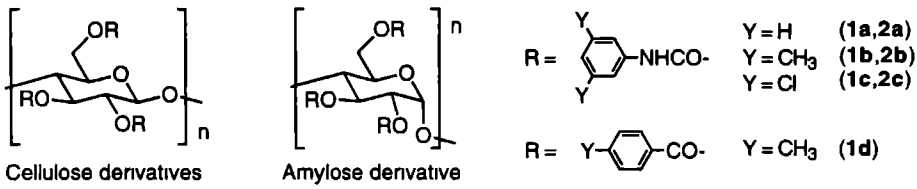


Figure 7 1

Okamoto and coworkers reported that phenylcarbamates and benzoate esters of various polysaccharides, such as cellulose, amylose chitosan, xylan, curdlan and inulin showed characteristic chiral recognition ability as stationary phases for HPLC when supported on silicagel [10] It was found that substituents attached to the phenyl groups influenced the chiral recognition ability considerably and either 3,5-dimethylphenyl carbamate (**1b**) or 3,5-dichlorophenyl carbamate (**1c**) exhibited higher resolving power for many racemic compounds than **1a** [11] In a later study they reported the use of amylose tris(3,5-dimethylphenyl carbamate) (**2b**) and tris(3,5-dichlorophenyl carbamate) (**2c**) as chiral stationary phases (CSP) upon adsorption over silica gel [12] At the moment cellulose **1b**, **1d** (3-methylbenzoate ester) and amylose **2b** are commercially available from Daicel Chemical Industries as Chiralcel OD, Chiralcel OJ and Chiralpak AD columns, respectively

In order to determine the resolution of enantiomers on a chiral column, capacity factors (k_R') and separation factors (α) have to be determined

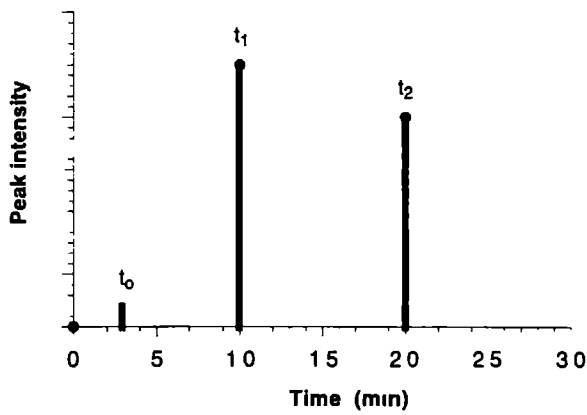
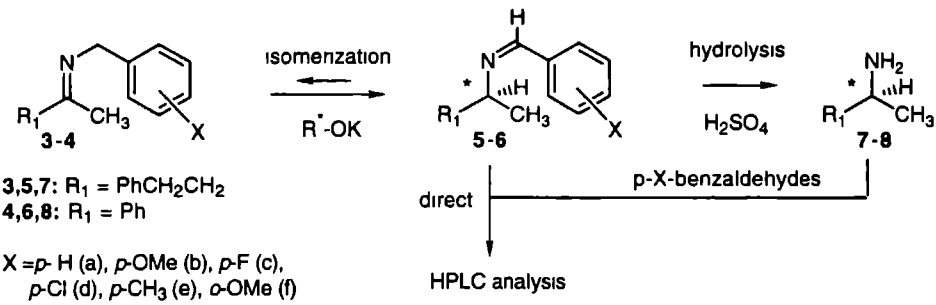


Figure 7 2

The capacity factors (k_R') were calculated using the equation $k' = (t_R-t_o) / t_o$ where t_R is the elution time and t_o is the void volume The separation factor (α) was calculated using the equation $\alpha = k_2'/k_1'$ where k_1' and k_2' are the capacity factors for the first and second eluted peaks, respectively (Figure 7 2)

The synthesis of optically active amines is of considerable interest since they occur in natural products and in various molecules with biological activities One of the routes in the preparation of

these compounds is the asymmetric reductive amination of a prochiral ketone [13] An alternative route involves imine intermediates in the asymmetric [1,3]-proton shift reaction using chiral bases (Scheme 7 1) This asymmetric imine isomerization reaction using chiral bases has been reported by Soloshonok et al [14] and Willems et al [15] in 1994 and 1995, respectively The results of the enantioselective [1,3]-proton transfer in the azaallylic system of *N*-benzylimines **3d** and **4a** catalyzed by chiral bases, producing the thermodynamically favored *N*-benzylidene derivatives **5d** and **6a**, respectively, are described in chapter 6



Scheme 7 1

It was extremely important to have access to a fast and accurate method for the determination of the enantiopurity of the product imines **5a-f** and **6a-f** during the isomerization reaction Furthermore, it would be useful if the ratio of the achiral imines **3a-f** and **4a-f** and chiral imines **5a-f** and **6a-f** could be determined simultaneously Additional information on the reaction mechanism of the imine isomerization reaction could be obtained by monitoring the racemization rate during the isomerization of enantiopure imines **5a-f** and **6a-f**, respectively These *p*-substituted model imines **5a-f** and **6a-f** (X = *p*-H, *p*-OMe, *p*-F, *p*-Cl, and *p*-Me) were also applied in a Hammett analysis of the reaction of interest (chapter 5) Finally, the determination of the e e 's of the product amines **7** and **8**, after hydrolysis of imines **5a-f** and **6a-f**, was of interest The isomerization, hydrolysis and derivatization of the compounds of interest is shown in Scheme 7 1

To obtain the aforementioned information on the enantiopurity of model imines **5a-f** and **6a-f** the resolution behavior of these imines using HPLC techniques with different commercially available chiral columns was examined For the compounds studied, no literature data on direct HPLC methods were available For the enantiomeric analysis of diimines, a direct HPLC method on a cellulose based CSP has been reported [16]

7.2 Results and discussion

The results obtained with the Chiralpak AD, Chiralcel OD-H and Chiralcel OJ columns with respect to the separation of the enantiomers of imines **5a-f** and **6a-f** are collected in Tables 7 1 and 7 2, respectively All *p*-substituted model imines **5a-f** could be separated (α>1 10) when the Chiralpak AD column was applied However, for the *p*-F imine **5c** and the p-Me imine **5e** no base line resolution was obtained under the HPLC conditions used (*n*-hexane/2-propanol 98 2) When the eluent was changed to *n*-hexane/2-propanol 99 1 both imines **5c** and **5e** were resolved with base line resolution The *p*-F imine **5c** could not be resolved using the Chiralcel OD-H and the Chiralcel OJ columns, and no resolution was obtained for the *p*-Me imine **5e** using the Chiralcel OJ column However, the *p*-Me imine **5e** was well resolved when the Chiralcel OD-H column was applied All *p*-substituted model imines **6a-f** could be separated (α>1 20) when the Chiralpak AD column was applied The *o*-methoxy imine **6f** could not be resolved using the Chiralcel OD-H and the Chiralcel OJ columns No resolution was obtained for the *p*-F imine **6c** using the Chiralcel OD-

H column.

Table 7.1 Capacity factors (k') and selectivities (α) of imines **5a-f** enantiomers

Imine	X	Chiralpak AD		Chiralcel OD-H		Chiralcel OJ	
		k'[a]	α	k'[a]	α	k'[a]	α
5a	*p*-H	0.73	1.30	1.40	1.95	1.04	1.28
5b	*p*-OCH_3	1.72	1.47	4.80	1.25	2.21	1.50
5c	*p*-F	0.76	1.13	0.95	1.00	1.12	1.00
5d	*p*-Cl	0.81	1.18	0.93	1.06	1.11	1.35
5e	*p*-CH_3	0.81	1.10	1.28	1.59	1.14	1.00
5f	*o*-OCH_3	0.95	1.15	3.20	1.59	1.41	1.53

Mobile phase. n-hexane-2-propanol (90:10) for Chiralcel OJ and n-hexane-2-propanol (98:2) for Chiralcel OD-H and Chiralpak AD. For other conditions, see experimental part. a) Capacity factor (k') of the first eluted enantiomer.

From these data it is clear that the *p*-X substituent of model imines **5a-f** and **6a-f** has a marked effect on both the retention and the enantioselectivity of the analytes. The Chiralpak AD column showed enantioselectivity for all analyzed *p*-substituted imines **5a-f** and **6a-f**. Moreover, it was the only chiral stationary phase (CSP) that showed enantioselectivity toward the *o*-methoxy substituted imine **6f**. The elution order of the enantiomers **5a-f** and **6a-f** on the Chiralpak AD column was found to be: imines **5a-f** (R before S) and **6a-f** (S before R).

Table 7.2 Capacity factors (k') and selectivities (α) of imines **6a-f** enantiomers

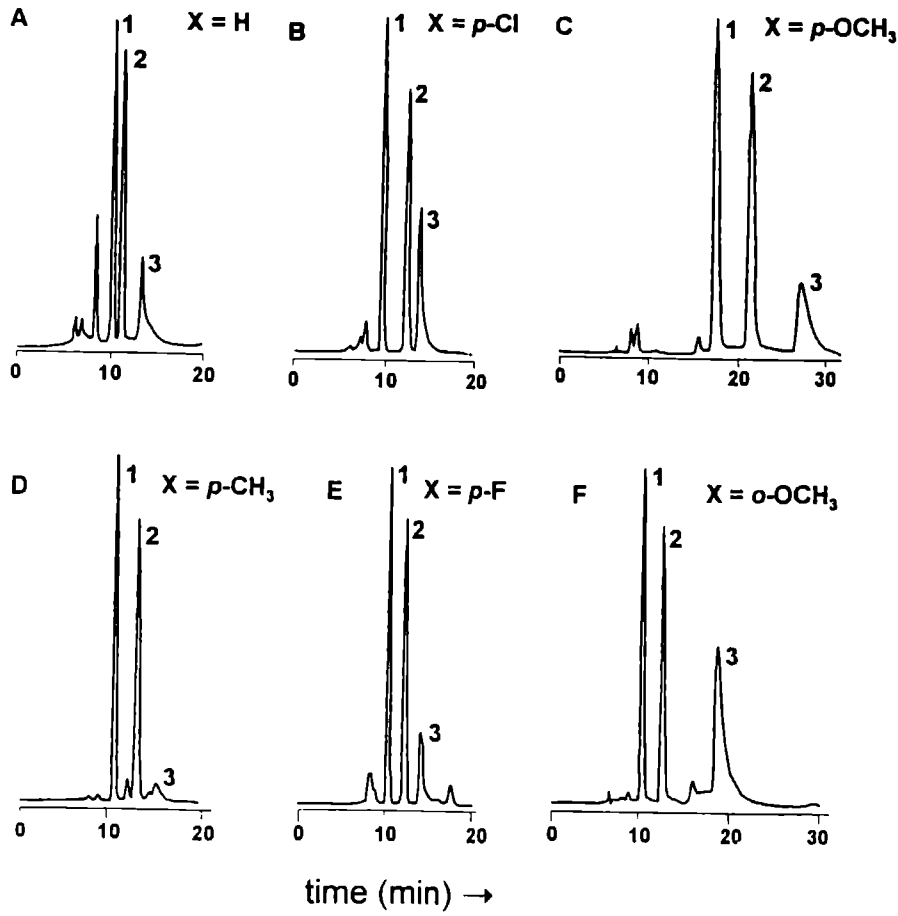
Imine	X	Chiralpak AD		Chiralcel OD-H		Chiralcel OJ	
		k'[a]	α	k'[a]	α	k'[a]	α
6a	H	1.03	1.20	1.25	1.69	2.36	1.33
6b	*p*-OCH_3	2.46	1.28	2.83	1.37	5.14	1.11
6c	*p*-F	1.03	1.35	0.95	1.00	3.29	1.15
6d	*p*-Cl	1.13	1.48	0.97	1.07	2.16	1.26
6e	*p*-CH_3	1.14	1.40	1.10	1.45	2.32	1.16
6f	*o*-OCH_3	1.04	1.40	1.75	1.00	4.39	1.00

Mobile phase: n-hexane-2-propanol (90:10) for Chiralcel OJ and n-hexane-2-propanol (98.2) for Chiralcel OD-H and Chiralpak AD. For other conditions, see experimental part. a) Capacity factor (k') of the first eluted enantiomer.

In addition to the determination of the enantiomeric excess, the monitoring of the percentage of conversion during the imine isomerization process was essential. The conversion can be determined by GC as has been shown previously.[4] However, it would be more advantageous to determine conversion and enantiomeric excess by the same method. Therefore, the chromatographic behavior of the achiral starting imines **3a-f** and **4a-f** was evaluated on the Chiralpak AD column using the same conditions as for the chiral imines **5a-f** and **6a-f**. It was found that at the detection wavelength (254 nm) conjugated imines **4a-f** and **6a-f** could be analyzed and the ratio of imines **4a-f** and **6a-f** (after correction for the difference in extinction coeffients) as well as the enantioselectivity could be monitored simultaneously. Separation of all *p*-substituted imine isomers **4a-f** and the enantiomers of imines **6a-f** was possible using the Chiralpak AD column. In all cases the achiral imines **4a-f** showed a higher retention than the chiral imines **6a-f**. Typical chromatograms are shown in Figure 7.4. However, for model imines **3a-f** and **5a-f** the non-conjugated starting imines **3a-f** could not be detected at the applied wavelength (254 nm) and therefore, only the enantiomeric excess of imines **5a-f** and not the ratio of imines **3a-**

f and **5a-f** could be determined (Figure 7.5). The fact that the starting material could not be monitored at the concentration level employed is due to the low extinction coefficients of imines **3a-f** in the high UV-region (> 220 nm).

Figure 7.4 HPLC chromatograms of imines **4a-f** and the enantiomers of imines **6a-f**



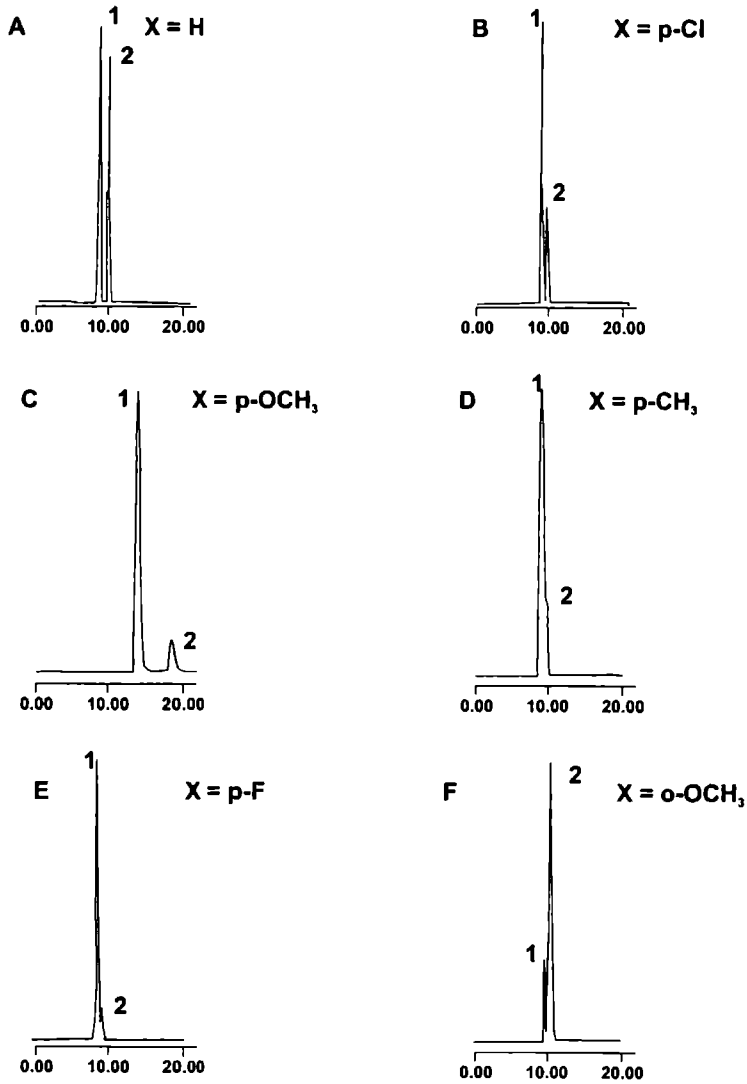
Column: Chiralpak AD. Mobile phase: n-hexane/2-propanol (98:2). For other conditions, see Experimental. Peak 1: (S)-imine **6a-f**; peak 2: (R)-imine **6a-f**; peak 3: imine **4a-f**. X denotes the substituent (see Scheme 7.1).

To investigate whether racemization occurs during the hydrolysis and work-up of imines **5a-f** and **6a-f**, a method to determine the enantiomeric excess of amines **7** (R_1=$PhCH_2CH_2$) and **8** (R_1=Ph) was essential. Initially, the e.e.'s of amine **7** were determined with the use of Mosher derivatives[17] and for amine **8** camphanic acid [18] or Mosher derivatives were applied. The Mosher and camphanic acid derivatives of amines **7** and **8** were analyzed by GLC.

An improved method for this analysis is the derivatization of amines **7** and **8** with p-X substituted benzaldehydes, resulting in imines **5** and **6**, respectively (Scheme 7.1) and subsequent analysis by HPLC using the Chiralpak AD column. From the results in Tables 7.1 and 7.2 it can be concluded, that the highest enantioselectivities for model imines **5a-f** and **6a-f** were obtained

using the Chiralpak AD column. For *p*-H and *p*-OMe substituted model imines **5a** and **5b** separation factors (α) of 1.30 and 1.47, respectively, were calculated. Therefore, benzaldehyde and *p*-methoxy benzaldehyde were used as the reagents of choice in order to determine the enantiopurity of 4-phenyl-2-amino butane (**7**). The best separation factor (1.48) for model imines **6a-f** was obtained for the *p*-Cl substituted imine **6d**. Therefore, *p*-Cl-benzaldehyde was applied in the analysis of the enantiopurity of chiral amine **8**.

Figure 7.5 HPLC chromatograms of the enantiomers of imines **5a-f**



Column: Chiralpak AD. Mobile phase: n-hexane/2-propanol (98:2). For other conditions, see Experimental. Peak 1: (R)-imine **5a-f**; peak 2: (S)-imine **5a-f**. X denotes the substituent (see Scheme 7.1).

Upon analysis of the derivatives (see experimental), the presence of the excess *p*-substituted benzaldehydes did not interfere with the elution of the imine enantiomers **5a-b** and **6d**. In all cases the *p*-substituted benzaldehydes showed a higher retention than the chiral imines **5a-b** and **6d**.

7.3 Conclusions

A high-performance liquid chromatographic method has been developed for the analysis of the intermediates and end products in an asymmetric isomerization route toward optically active amines **7** and **8**. The commercially available cellulose-based chiral stationary phases Chiralpak AD, Chiralcel OD-H, Chiralcel OJ were evaluated. All *p*-substituted imine enantiomers **5a-f** and **6a-f** could be readily resolved with selectivities (α) higher than 1.10 using the Chiralpak AD column.

For the separation of the achiral imines **4a-f** from the chiral imine enantiomers **6a-f**, best results were obtained on the Chiralpak AD column.

By derivatization with ring substituted benzaldehydes, the enantiopurity of 4-phenyl-2-aminobutane (**7**) and α-methylbenzylamine (**8**) could be determined using the same method.

7.4 Experimental section

General Methods The chromatographic system consisted of a Gilson (Villiers-le-Bel, France) Model 302 pump and Gilson Model 231-401 autosampler for injection. The injection loop had a 20-µl capacity. The columns used were Chiralcel OD-H and OJ (250*4.6 mm I.D) and Chiralpak AD (250*4.6 mm I.D.) from J T. Baker (Deventer, The Netherlands). The flow-rate was 0 50 ml/min and the columns were operated at ambient temperature The column effluent was monitored with a Waters (Milford, MA, USA) Model 481 UV detector set at 254 nm UV, NMR and GC-MS techniques were used for characterization of the Schiff base derivatives of 4-phenyl-2-amino butane (**7**) and α-methylbenzylamine (**8**). UV spectra of Schiff base derivatives were recorded with a Perkin-Elmer Lamba 5 UV/Vis spectrofotometer. ^{1}H and ^{13}C NMR analysis of Schiff base derivatives was performed with a Bruker (Karlsruhe Germany) AM 100 instrument. For GC-mass spectrometry, a Varian Saturn benchtop GC-MS apparatus with a Varian 8100 autosampler was used MS analysis was performed using electron impact (EI)

Chemicals. (±)- and (R)-(+)-α-methylbenzylamine, benzaldehyde, 4-methylbenzaldehyde, 4-methoxybenzaldehyde, 4-fluorobenzaldehyde and 4-chlorobenzaldehyde were obtained from Acros Chimica (Geel, Belgium) (±)- and (R)-(+)-4-phenyl-2-aminobutane were obtained from DSM-Andeno (Venlo, the Netherlands) HPLC-grade 2-propanol and *n*-hexane were purchased from Merck (Darmstadt, Germany). All other chemicals were of analytical reagent grade and were used as received.

Imine synthesis

All imines were prepared according to procedures described in chapter 5

Hydrolysis of imines 5a-f and 6a-f

The crude reaction products were hydrolyzed using 2M H_2SO_4 in a mixture of THF and ether for 24h The reaction was monitored using GLC. The amines **7** and **8** were separated from the aldehydes by acid-base extraction procedure and the combined organic layers were dried ($MgSO_4$) and concentrated. The enantiopurity of the product amines **7** and **8** was determined using HPLC (Chiralpak AD) according to a procedure as described below.

Derivatization of amines 7 and 8

About 1 mg of 4-phenyl-2-amino butane (**7**) or α-methylbenzylamine (**8**) was dissolved in 1 ml of diethyl ether *p*-X substituted benzaldehyde (2 mg) was added together with 500 mg of $MgSO_4$. After standing for 30 minutes at roomtemperature, a 20-µl volume of the reaction mixture was diluted with n-hexane / 2-propanol (98:2) and an aliquot of this solution was injected into the HPLC system. The reaction products were analyzed by means of ^{1}H and ^{13}C NMR and GC/MS techniques. Both NMR and GC/MS data showed that the formation of the Schiff base had occurred with a complete conversion of the starting material into the corresponding imines **5a-b** and **6d** within 30 min. No *syn-anti* isomers could be observed by means of NMR.

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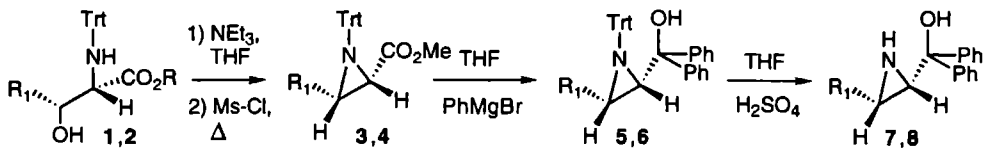
The research described in this thesis can be devided into two parts. The first part describes the design, and synthesis of a new class of chiral catalysts derived from aziridine-2-carboxylic esters, *viz.* the aziridine-2-carbinols. The asymmetric reduction of prochiral ketones using 1,3,2 oxazaborolidines derived from aziridine-2-carbinols has been investigated.

The second part is devoted to a kinetic study of the imine isomerization reaction and the development of an asymmetric catalytic version of this reaction.

In chapter 1 a general introduction on chirality and methods to obtain enantiomerically enriched compounds is presented.

In chapter 2 the pertinent literature on the design and use of chiral catalysts in the preparation of chiral alcohols and amines is briefly surveyed. The major parts of this survey are devoted to the enantioselective reduction of prochiral ketones using chiral 1,3,2 oxazaborolidines and on mechanistic studies of the imine isomerization reaction as described by Ingold in the 1930s, Ossorio in the 1950s and Cram in the1960s.

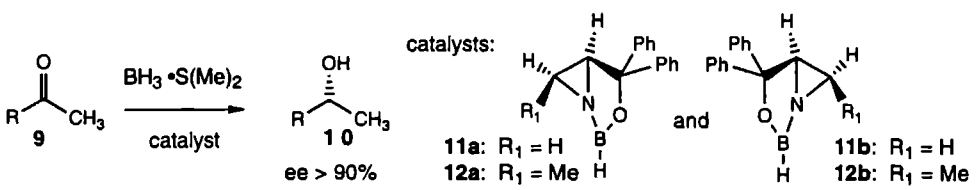
In chapter 3 a convenient multigram 'one pot procedure' for the synthesis of *N*-trityl-aziridine-2-carboxylic esters **3** and **4** starting from the *N*-trityl methyl esters of L-serine **1**, and L-threonine **2** using methanesulfonyl chloride and triethylamine is presented. The *N*-trityl-aziridine-2-carbinols **5** and **6** are prepared from the corresponding *N*-trityl-aziridine-2-carboxylic esters **3** and **4** using a Grignard or an alkyllithium reaction, as depicted in Scheme 8.1.



1,3,5,7: R_1=H, from L and D-serine
2,4,6,8: R_1=Me, from L and D-threonine

Scheme 8.1

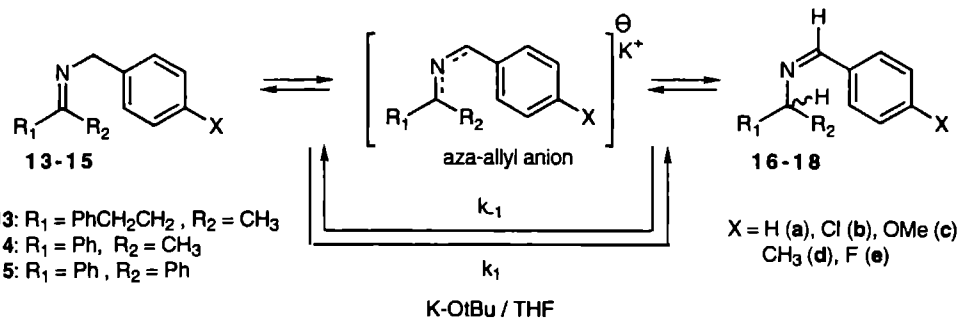
An X-ray analysis of aziridine-2-carbinols **5** and **6** revealed that the diphenyl carbinol units and the trityl groups have a *trans* relationship, and that there is an intramolecular hydrogen bond between the aziridine nitrogen and carbinol hydroxyl group. According to temperature dependent ^{1}H NMR analysis a hydrogen bond is also present in solution. The enantiomeric purity of the *N*-trityl aziridine-2-carbinols **5** and **6** was determined using HPLC techniques and was higher than 99% in both cases. The *N*-trityl-aziridine-2-tertiairy alcohols **5** and **6** were applied as catalysts in the asymmetric imine isomerization reaction (chapter 6) and the potassium alcoholates derived therefrom turned out to be the best catalysts in this particular reaction. The *N*-trityl-aziridine-2-tertiairy alcohols **5** and **6** could be converted into the corresponding deprotected aziridine-2-tertairy alcohols **7** and **8** with sulfuric acid in methanol/THF.



Scheme 8.2

The asymmetric reduction of prochiral ketones **9** to chiral secondary alcohols **10** by 1,3,2-oxazaborolidines derived from aziridine-2-tertiairy alcohols **7** and **8** is described in chapter 4 (Scheme 8.2). Enantioselectivities of up to 95% were obtained with these reagents. The stereoselectivity of the reaction depends both on the temperature during the reduction and on the conditions during the preparation of the chiral oxazaborolidines.

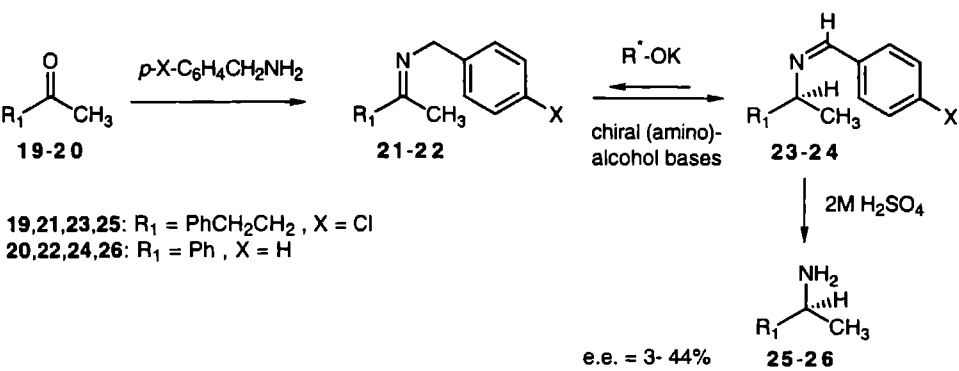
In chapter 5 the kinetics of the [1,3]-proton transfer in the azaallylic system of N-benzylimines **13-15** catalyzed by K-OtBu, which results in the formation of thermodynamically favored N-benzylidene derivatives **16-18** are described (Scheme 8.3). The imine isomerization reaction can be described by 1st order equilibrium kinetics. By performing the imine isomerization reaction at different temperatures, the activation energy using the Arrhenius relationship, the overall thermodynamic parameters ΔH, ΔS and ΔG using the standard molar free Gibbs function, and the energy parameters of activation $\Delta H^{\#}$, $\Delta S^{\#}$ and $\Delta G^{\#}$ using the Eyring relationship were determined.



Scheme 8.3

Several *p*-substituted imines were used as substrates in this isomerization reaction and these experiments led to Hammett plots of the imine modelsystems **13-15**. Important information on the imine isomerization could be obtained when the racemization of enantiomerically pure product imines **16b** and **17b** was monitored.

From the results obtained in chapter 5 it could be concluded that aza-allyl anions play an essential role in the imine isomerization reaction. Furthermore, it was found that intimate ion pairs ought to be present as intermediates during the isomerization.



Scheme 8.4

In chapter 6 the asymmetric catalytic synthesis of chiral amines using a chiral base catalyzed [1,3]-proton shift reaction of imines is described. The isomerization reaction of N-benzylimines **21**

and **22** derived from prochiral ketones (benzylacetone, acetophenone) and *p*-substituted benzylamines, is catalyzed by chiral alcohols and aminoalcohols **27-41** and gives enantiomerically enriched N-benzylidene derivatives **23** and **24** (up to 44% e e) The resulting products **23** and **24** are readily hydrolyzed to the corresponding amines **25** and **26** in good yields (Scheme 8 4)

The applied chiral alcohols and aminoalcohols in the asymmetric isomerization reaction are collected in Figure 8 1 The best results were obtained with the potassium alcoholates derived from the new catalysts *N*-trityl-azirdine-2-carbinols **36** and **40** Interestingly, the catalyst derived from L-serine was the best catalyst in the isomerization of imine **21** (e e = 44%), whereas the aziridine carbinol from L-threonine gave the best results for imine **22** (e e = 34%) The asymmetric induction can be explained by involving a chirality transfer in the intimate ion pair of the intermediate aza-allyl anion and the chiral amino alcoholates

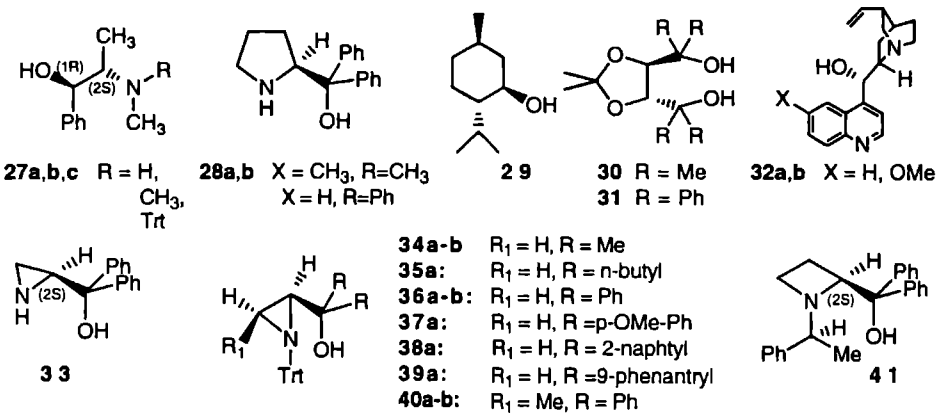
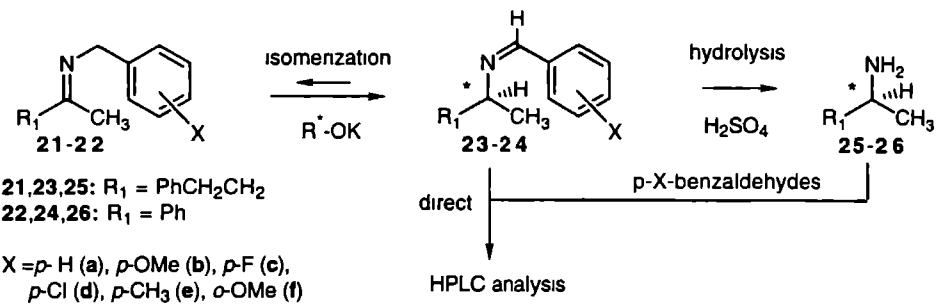


Figure 8 1

In chapter 7 a high-performance liquid chromatographic method for the analysis of the imine intermediates and end-products in the asymmetric isomerization route toward optically active amines **25** and **26** is described (Scheme 8 5)



Scheme 8 5

The commercially available cellulose-based chiral stationary phases Chiralpak AD, Chiralcel OD-H, Chiralcel OJ were used All *p*-substituted imine enantiomers **23a-f** and **24a-f** could be readily resolved with selectivities (α) higher than 1 10 using the Chiralpak AD column For the separation of the achiral imines **21a-f** and **22a-f** from the chiral imine enantiomers **23a-f** and **24a-f**, best results were also obtained on the Chiralpak AD column

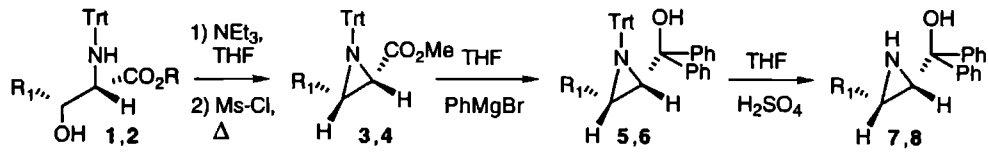
By derivatization with ring-substituted benzaldehydes, the enantiomeric purity of 4-phenyl-2-amino butane (**25**) and α-methylbenzylamine (**26**) could be determined using the same method

Het onderzoek dat is beschreven in dit proefschrift bestaat uit twee gedeeltes In het eerste gedeelte wordt het onderzoek naar het ontwerp en de synthese van een nieuwe klasse van chirale katalysatoren afgeleid van aziridine-2-carbonzure esters, *nl* the aziridine-2-carbinolen, beschreven Verder worden in dit gedeelte de resultaten van asymmetrische reductie van prochirale ketonen door middel van 1,3,2 oxazaborolidines, afgeleid van de voornoemde aziridine-2-carbinolen, vermeld

In het tweede gedeelte wordt een kinetische studie gepresenteerd van de imine isomerisatie reactie en worden de mogelijkheden van een asymmetrische katalytische versie van deze reactie verkend

In hoofdstuk 1 wordt een algemene introductie gegeven over chiraliteit en de verschillende methoden om enantiomeer zuivere verbindingen te bereiden

In hoofdstuk 2 wordt een kort overzicht van de relevante literatuur gepresenteerd over het ontwerp en het gebruik van chirale katalysatoren bij de bereiding van chirale alcoholen en amines In dit overzicht wordt vooral aandacht geschonken aan de enantioselectieve reductie van prochirale ketonen met behulp van chirale 1,3,2 oxazaborolidines en aan het mechanisme van de imine-isomerisatie-reactie, zoals beschreven door Ingold in de jaren '30, Ossorio in de jaren 50 en Cram in de jaren '60



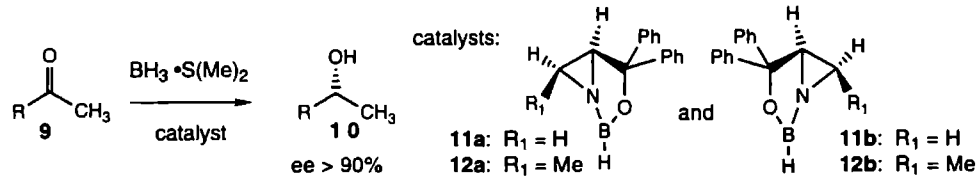
1,3,5,7 R_1=H, uit L en D-serine
2,4,6,8 R_1=Me, uit L en D-threonine

Schema 8 1

In hoofdstuk 3 wordt een eenvoudige op multigram schaal toepasbare 'één-pots procedure' voor de bereiding van *N*-trityl-aziridine-2-carbonzure esters **3** en **4** beschreven (Schema 8 1) Hierbij worden *N*-trityl-methyl esters van L-serine **1** en L-threonine **2** in hoge opbrengst en zuiverheid omgezet in de doelmoleculen **3** en **4**, gebruikmakende van methaansulfonylchloride en triethylamine in THF als oplosmiddel Vervolgens worden **3** en **4** via een Grignardreactie of een alkyllithiumreactie omgezet in de *N*-trityl-aziridine-2-carbinolen **5** and **6** Met behulp van X-ray diffractie-analyse aan de aziridine-2-carbinolen **5** and **6** kon worden vastgesteld dat de difenylcarbinol-groepen en de trityl-groepen een *trans*-orientatie ten opzichte van elkaar bezitten Verder bleek dat er in beide aziridine-2-carbinolen **5** en **6** een intramoleculaire waterstofbrug aanwezig is Uit temperatuur-afhankelijke ^{1}H NMR experimenten bleek dat deze waterstofbrug ook in oplossing aanwezig is De enantiomere zuiverheid van de *N*-trityl aziridine-2-carbinolen **5** and **6** werd bepaald met HPLC en bleek voor beide katalysatoren hoger dan 99% te zijn

De *N*-trityl-aziridine-2-tertiaire-alcoholen **5** en **6** werden ingezet als katalysatoren in de asymmetrische imine isomerisatie reactie (hoofdstuk 6) en de kalium alcoholaten afgeleid van deze verbindingen gaven de hoogste chirale inductie in deze reactie De *N*-trityl-aziridine-2-tertiaire alcoholen **5** and **6** konden met behulp van zwavelzuur in methanol/THF op eenvoudige wijze worden omgezet in de overeenkomstige onbeschermde aziridine-2-tertaire alcoholen **7** and **8** (Schema 8 1)

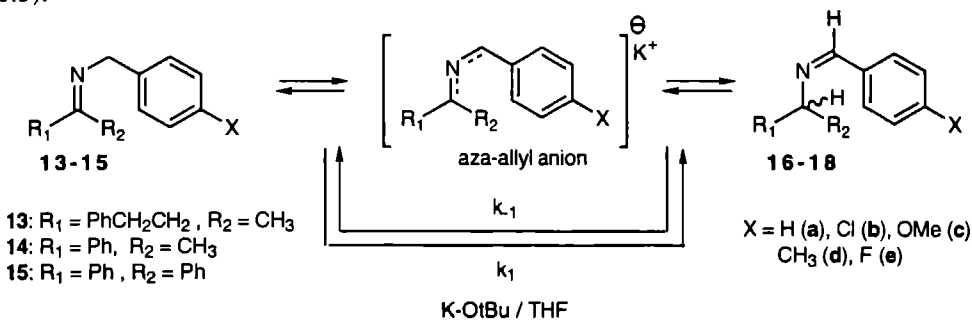
De asymmetrische reductie van prochirale ketonen **9** tot chirale secundaire alcoholen **10** met behulp van 1,3,2-oxazaborolidines afgeleid van aziridine-2-tertiaire-alcoholen **7** and **8** wordt beschreven in hoofdstuk 4 (Schema 8.2).



Schema 8.2

Met behulp van de beschreven katalysatoren (*vide supra*) konden chirale inducties tot 95% worden verkregen. De enantioselectiviteit van de reactie bleek ondermeer afhankelijk van de temperatuur tijdens de reductie en de reactiecondities tijdens de bereiding van de chirale oxazaborolidines.

In hoofdstuk 5 zijn kinetische studies aangaande de imine-isomerisatie van N-benzylimines **13-15** naar de thermodynamisch stabielere N-benzylidene derivatives **16-18** beschreven Schema 8.3).



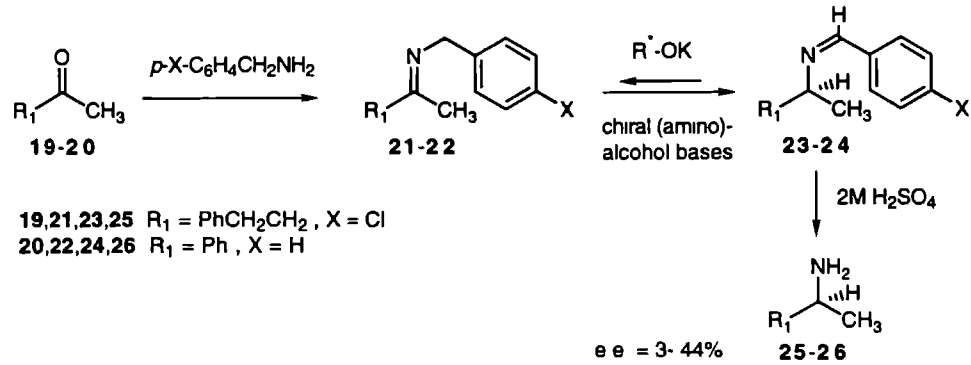
Schema 8.3

De imine-isomerisatie-reactie kan worden beschreven met behulp van 1ste orde evenwichtskinetiek. Door bestudering van de isomerisatie-reactie bij verschillende temperaturen konden gebruikmakend van de Arrhenius-vergelijking de activeringsenergie, gebruikmakend van de vrije-Gibbs-energie vergelijking de overall thermodynamische parameters ΔH, ΔS en ΔG en gebruikmakend van de Eyring-vergelijking de activeringsparameters $\Delta H^{\#}$, $\Delta S^{\#}$ and $\Delta G^{\#}$ worden bepaald.

Hammett plots werden verkregen door *p*-gesubstitueerde modelimines **13-15** als substraat in te zetten tijdens de isomerisatie-reactie. Racemisatie-experimenten met enantiomeer-zuivere produkt-imines **16b** en **17b** leverde belangrijke aanvullende informatie op omtrent het mechanisme van de isomerisatie-reactie. Uit de resultaten, zoals die worden beschreven in hoofdstuk 5 kan worden geconcludeerd dat aza-allyl anionen een essentiële rol spelen in de imine-isomerisatie-reactie. Verder bleek dat tijdens de imine isomerisatie waarschijnlijk intieme-ionen paren aanwezig zijn, die essentieel zijn om naderhand asymmetrische inductie mogelijk te maken.

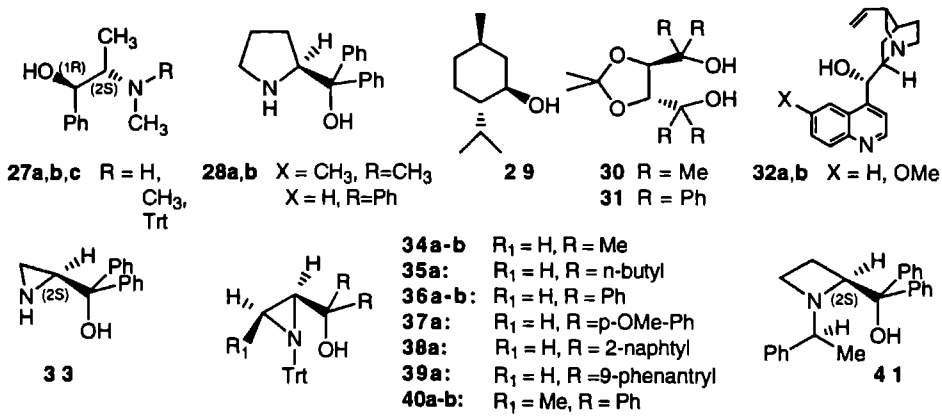
In hoofdstuk 6 wordt de bereiding van chirale amines met behulp van de door chirale basen gekatalyseerde asymmetrische imine-isomerisatie-reactie beschreven. De isomerisatie van N-benzylimines **21** en **22** afgeleid van prochirale ketonen (benzylaceton, acetofenon) en *p*-gesubstitueerde benzylamines, werd gekatalyseerd door chirale alcoholen en aminoalcoholen **27-41** (Figuur 8.1) en tijdens deze reacties werd een maximale chirale inductie in de synthese van N-benzylidene derivaten **23** en **24** van 44% bereikt. De verkregen imine-produkten **23** en **24**

konden op eenvoudige wijze en in goede opbrengsten worden gehydrolyseerd tot de overeenkomstige amines **25** en **26** (Schema 8 4)



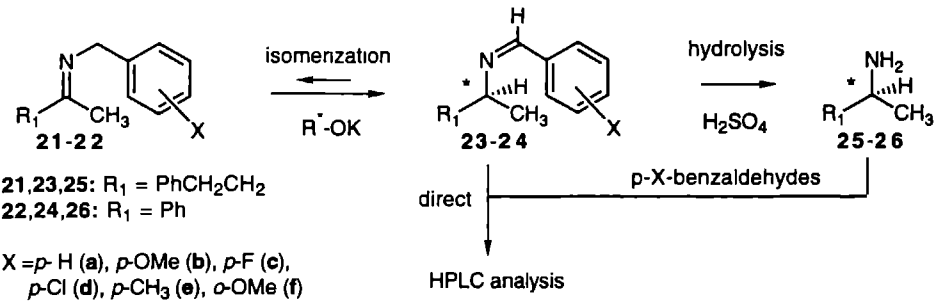
Schema 8 4

De hoogste chirale inducties werden bereikt met de kalium alcoholaten afgeleid van de nieuwe *N*-trityl-azirdine-2-carbinolen **36** en **40** Opvallend was dat de katalysator afgeleid van L-serine de beste resultaten leverde voor modelimine **21** (e e = 44%), terwijl de aziridine-carbinol afgeleid van L-threonine de hoogste inducties gaf in de isomerisatie van imine **22** (e e = 34%) De asymmetrische inductie kan worden verklaard met behulp van chiraliteitsoverdracht in het intieme ionenpaar van aza-allyl anionen en de amino alcoholaten



Figuur 8 1

In hoofdstuk 7 wordt een HPLC methode beschreven voor een snelle en betrouwbare analyse van de enantiomere overmaat van de produkt-imines **23** en **24**, de amine-produkten **25** en **26** en de conversie van imines **21-22** in **23-24** tijdens het asymmetrische imine-isomerisatie-proces (Schema 8 5) De op basis van cellulose commercieel verkrijgbare chirale stationaire fases Chiralpak AD, Chiralcel OD-H, Chiralcel OJ werden getest Bij gebruik van de Chiralpak AD kolom kon een goede resolutie ($\alpha > 1$ 10) worden verkregen voor alle *p*-gesubstitueerde imine-enantiomeren **23a-f** en **24a-f** Na derivatisering met ring-gesubstitueerde benzaldehydes, kon de enantiomere zuiverheid van zowel 4-fenyl-2-amino-butaan (**25**) als α-methylbenzylamine (**26**) worden bepaald met behulp van dezelfde procedure


isomerization
R*-OK
hydrolysis
H2SO4
21-22
23-24
25-26
21,23,25: R1 = PhCH2CH2
22,24,26: R1 = Ph
X =p- H (a), p-OMe (b), p-F (c),
p-Cl (d), p-CH3 (e), o-OMe (f)
direct
p-X-benzaldehydes
HPLC analysis

Schema 8.5

Publications and Presentations

1. Synthesis of Functionalized Amino Acids by Ring-opening Reactions of Aliphatically Substituted Aziridine-2-carboxylic Esters

   Legters, J , Willems, J G H , Thijs, L , Zwanenburg, B , *Recl Trav Chim Pays-Bas*, **1992**, *11*, 59-68

2. Synthesis of Functionalized Amino Acid Esters from Aziridine-2-carboxylic Esters

   Willems, J G H , Legters J , Thijs L , Zwanenburg, B , *Book of Abstracts, 23rd Congress of Heterocyclic Chemistry*, Nagoya, Japan, October 1992, p 269

3. Synthesis and Crystal Structure of Enantiopure N-Trityl-Aziridine-2-Carbinols from L-Serine and L-Threonine

   Willems, J G H , Hersmis, M C , de Gelder, R , Smits, J M M , Hammink, J B , Dommerholt, F J , Thijs, L , Zwanenburg, B , *J Chem Soc , Perkin Trans 1*, **1996**, submitted for publication (Chapter 3, this thesis)

4. Asymmetric Ketone Reduction using Oxazaborolidines derived from Azindine Carbinols

   Willems, J G H , Hammink, J B , Vaarhorst, A M , Dommerholt, F J , Thijs, L , Zwanenburg, B , *Tetrahedron Lett* , **1995**, *36*, 603 (Chapter 4, this thesis)

5. Asymmetric Reduction of Prochiral Ketones using Chiral Oxazaborolidines derived from Azindine Carbinols

   Willems, J G H , Hammink, J B , Dommerholt, F J , Thijs, L , Zwanenburg, B , in preparation (Chapter 4, this thesis)

6. Asymmetric Ketone Reduction using Oxazaborolidines derived from Azindine Carbinols

   Willems, J G H , Hammink J B , Vaarhorst, A M , Dommerholt, F J , Thijs, L , Zwanenburg, B , oral poster presentation at the *5th International Symposium on Chiral Discrimination*, Stockholm, Sweden, september 1994 (Chapter 4, this thesis)

7. Imine Isomerisation Reaction: a Kinetic Study

   Willems, J G H , Husken, H , Lucassen, A C B , Hersmis, M C , de Vries, J G , Nolte, R J M , Zwanenburg, B , in preparation (Chapter 5, this thesis)

8. Asymmetric Imine Isomerisation in the Enantioselective Synthesis of Chiral Amines from Prochiral Ketones

   Willems, J G H , de Vries, J G , Nolte, R J M , Zwanenburg, B , *Tetrahedron Lett* , **1995**, *36*, 3917 (Chapter 6, this thesis)

9. Catalytic Enantioselective Synthesis of Chiral Amines via the Asymmetric Imine Isomerisation Reaction

   Willems, J G H Lucassen, A C B , Hersmis, M C , de Vries, J G , Nolte, R J M , Zwanenburg, B , in preparation (Chapter 6, this thesis)

10. High-performance Liquid Chromatography of Imine Isomers on Cellulose-based Chiral Stationary Phases

    Willems, J G H , Duchateau, A L L , Zwanenburg, B , in preparation (Chapter 7, this thesis)

Curriculum Vitae

De auteur van dit proefschrift werd geboren op 17 april 1966 te Nijmegen. Aldaar bezocht hij de NUTS-school (1972-1978) en het Elshof College (1978-1984) en behaalde in juni 1984 het V.W.O-B diploma. In hetzelfde jaar werd begonnen met de studie scheikunde aan de Katholieke Universiteit Nijmegen (KUN). In december 1990 werd het doctoraal examen afgelegd met als hoofdvak Organische Chemie (Prof. dr. B. Zwanenburg, L. Thijs, dr. J. Legters) waarbij de synthese van exotische aminozuren door middel van ringopenings reacties aan aziridine-2-carbonzure esters werd geëxploreerd. Het bijvak werd uitgevoerd op de afdeling Biofysische Chemie (Prof. dr. C.W. Hilbers, dr. M.M. Blommers, dr. J.A.L.I. Walters, J. Aelen) waarbij het thermodynamisch gedrag van DNA pseudoknopen door middel van U.V-smelt metingen werd onderzocht. In 1990 werd een extra bijvak stage vervuld aan de Universiteit van Bowling Green, USA (Prof. dr. D.C. Neckers, Prof. dr. W.R. Midden). Tijdens deze bijvakstage werd de "Bio-photochemistry" van DNA modelsystemen onderzocht. In de periodes september-december 1988 en september-december 1990 was hij als praktikum assistent betrokken bij het eerste jaars praktikum "Scheiding en Isolatie." Van januari tot mei 1990 was hij teaching assistent (TA) te Bowling Green (USA) (organic chemistry course 342).

Tijdens zijn studie was hij lid van de Nijmeegse Studenten Vereniging Carolus Magnus en vervulde in de periode van maart 1987 tot april 1988 de functie van vice-praeses nachtexploitatie in het sociëteitsbestuur (C.T.B.) van deze vereniging. In de periode 1985-1986 was hij lid van de Nijmeegse Studenten Roeivereniging PHOCAS en werd deelgenomen aan wedstrijden "regio-roeien" in een C4 (4 met stuurman).

Vanaf december 1990 tot en met december 1994 was hij als Assistent in Opleiding (A.I.O) verbonden aan het NSR Center for Molecular Structure, Design and Synthesis bij de vakgroep Organische Chemie. Het aldaar verrichte promotie onderzoek onder leiding van Prof. dr. B. Zwanenburg, Prof. dr. R.J.M. Nolte en dr. J.G. de Vries werd gesponsord door DSM Research (Geleen) en resulteerde uiteindelijk in dit proefschrift.

Vanaf 1 juli 1995 tot en met 1 april 1996 vervulde de auteur zijn militaire dienstplicht als ROAG-er (Reserve Officier Academisch Gevormd) bij de Koninklijke Luchtmacht te Den Haag.

Vanaf 1 juni 1996 is hij werkzaam bij GE-Plastics te Bergen op Zoom.